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Characterization and 1H-NMR applications of hexaaza macrocyclic complexes of lanthanides

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Characterization and ^{1}H-NMR Applications of Hexaaza Macrocyclic Complexes of Lanthanides

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Thesis

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ABSTRACT

Samples of $PrL(CH_3COO)_2Cl{\cdot}nH_2O$ (L=2,7,13,18,-tetramethyl-3,6,14,17,23,24-hexaazatricyclo[17.3.1.$1^{8,12}$] tetracosa-1(23), 2, 6, 8, 10, 12(24), 13, 17, 19, 21-decaene) were tested as lanthanide shift reagents using 1-heptanol, diisopropyl amine and hexylamine as substrates. These tests were unsuccessful. Syntheses of similar compounds with nitrate, carbonate, picrate, and chloroacetate counteranions were attempted in our desire to prepare template complexes with displaceable counteranions. A successful lanthanide shift reagent has not yet been synthesized.

INTRODUCTION

Nuclear magnetic resonance (NMR) is the most useful technique for organic structure determination. Briefly, ^{1}H- NMR reveals the number of nonequivalent protons present in a compound, the number of neighboring protons, and finally the total number of each type of protons (determined by integration).

As with any spectrometric technique, resolution is a major concern, especially when complex organic compounds are under investigation. One method to improve resolution would be to increase the strength of the applied magnetic field in order to separate overlappping chemical shifts of nonequivalent protons. However, this is a very expensive solution as high magnetic fields produced by sophisticated super-conducting systems are required. Fortunately, other methods exist.

Solvent induced shifts have proven to be useful in the simplification of NMR spectra. The established method of solvent shifts induced by pyridine was employed by Demarco(1) in 1968, to aid in the configurational and conformational analysis of several erythromycin aglycones. This method was helpful, but-induced shifts of δ 0.03 to 0.80ppm were obtained.

It had been known that paramagnetic ions would electrostatically

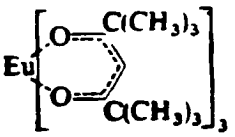
interact with electon rich substrates to cause NMR signal shifts, but they did not prove to be useful until 1969. Hinckley(2) at that time showed that the addition of a lanthanide metal in the form, $Eu(dpm)_3 \cdot 2pyridine$, (Fig # 1) to cholesterol monohydrate caused sizeable shifts in the proton resonances of cholesterol. The induced shifts, $(\nu_o - \nu)$, for the proton peaks of cholesterol in CCl_4 were δ -1.9 to -347.0 cps. Importantly, very little line broadening was observed. This was due to short relaxation times (with the exception of gadolinium). Moreover the general expectations were observed. For instance, induced shifts for protons in proximity to the point of association are larger than those farther away. The induced shifts are concentration dependent where the increase in shift is due to an increase in metal-complex concentration.

Sanders and Williams(3) in 1970 reported that the pyridine-free adduct, $Eu(dpm)_3$, is a superior shift reagent. The selective shifts observed in cholesterol were increased by a factor of four when this LSR (lanthanide shift reagent) was employed. Other organic substrates such as: alcohols, ketones, ethers, esters, and amines illustrated simplified first-order proton NMR spectra upon addition of $Eu(dpm)_3$. Sanders and Williams(3) further concluded that functional groups give downfield shifts in the order $-NH_2 > -OH > >C=O > -O- > -CO_2R > -CN$.

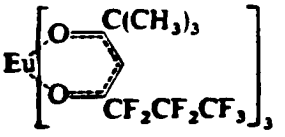
Due to these early reports of the capability of paramagnetic ions to aid in the simplification of ^1H- NMR spectra, the field of lanthanide shift reagents has expanded greatly.

As the name suggests, LSRs employ lanthanide metals to enhance the nonequivalence of nuclei to produce, in many cases, first-order proton NMR spectra. First order NMR spectra are those with large $\Delta\nu/J$ ratios, that is the chemical shift differences ($\Delta\nu$) in Hz is about ten times as great as J couplings for a pair of nuclei. In such cases singlets, doublets, triplets, etc. are observed. LSRs require three basic characteristics. First, the lanthanide metal cations must be paramagnetic. Second, these LSRs must function as Lewis-acids: the Lewis-acidic site is clearly the metal cation and these coordinate with the Lewis-base sites on the organic substrate. Third, the LSRs should be soluble in nonpolar organic solvents commonly used for NMR analysis(4).

It is helpful to examine the structure of a lanthanide shift reagent to appreciate the types of interactions taking place. The most prevalent LSRs are $Eu(dpm)_3$, where dpm refers to the tris-dipivaloylmethanato ligand, and $Eu(fod)_3$ where fod refers to the tris-6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctanedionato ligand.



$Eu(dpm)_3$



$Eu(fod)_3$

Figure 1

In both structures above, the Eu^{3+} lanthanide metal shows a coordination number of six and is thus attached to three bidentate ligands. The resonance forms above clearly illustrate that each oxygen is involved in a coordinate covalent bond where oxygen is donating electrons. These acetonylacetonate-type ligands enable the complex to be soluble in nonpolar NMR solvents such as CCl_4 and $CDCl_3$.

The short electron-spin relaxation times($<10^{-12}$sec) of Eu^{3+} ($4f^6$) along with Pr^{3+}($4f^2$) and Yb^{3+}($4f^{13}$) produce shifted NMR signals that are relatively narrow. On the other hand, Gd^{3+}($4f^7$) produces induced NMR signals that are broad and are no help to first-order NMR spectra. Finally, La^{3+} ($4f^0$) and Lu^{3+}($4f^{14}$) of the lanthanide series are diamagnetic and therefore are neither expected nor found to show lanthanide-induced shifts(5).

Paramagnetic ions exert a strong magnetic field of their own which has the capability of inducing shifts and thus spreading out NMR spectra. In order for this secondary magnetic field to be influential, the nucleus of the substrate must be in the vicinity of the cation(6). This is achieved due to the equilibria established in the following equation:

$$LSR + S = LSR{\cdot}S \qquad \text{where S = organic substrate}$$

This reversible interaction proceeds with great speed on the NMR time scale, and thus the NMR spectrum is due to a weighted average of S and LSR·S producing a single signal for each type of proton in the substrate.

The NMR solvent should be a nonpolar organic compound that is less Lewis-basic than the substrate in order to avoid competition between the substrate and solvent for the LSR(7).

The weighted average that produces an induced shift is referred to as the isotropic shift which has been discussed at great length by McConnell and Robertson. The total shift includes portions due to Fermi hyperfine contact interactions and to electron nuclear dipolar interactions (pseudocontact interactions)(6).

The pseudocontact mechanism is the main contributor to the paramagnetic induced shifts of protons. The pseudocontact mechanism can also be referred to as a dipole-dipole interaction. This type of interaction depends on the orientation of the paramagnetic cation and organic substrate. The modification of the McConnell-Robertson equation below illustrates this point(6).

$$\Delta\delta_{PC} = \frac{K(3\cos^2\theta - 1)}{r^3}$$

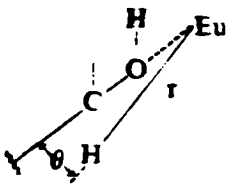
where $\Delta\delta_{PC}$ = the pseudocontact lanthanide induced shift.

K = a constant characteristic of the complex.

r = the length of a paramagnetic vector between the center of the nucleus of interest and the lanthanide cation.

θ = the angle between vector r and the principle magnetic axis of the complex.

The equation above is the one most frequently used.The principle magnetic axis is colinear with the axis through the center of the lanthanide cation and the substrate atom. Figure#2 illustrates this geometry using europium as the lanthanide metal and an alcohol as the organic substrate(5).



Figure#2

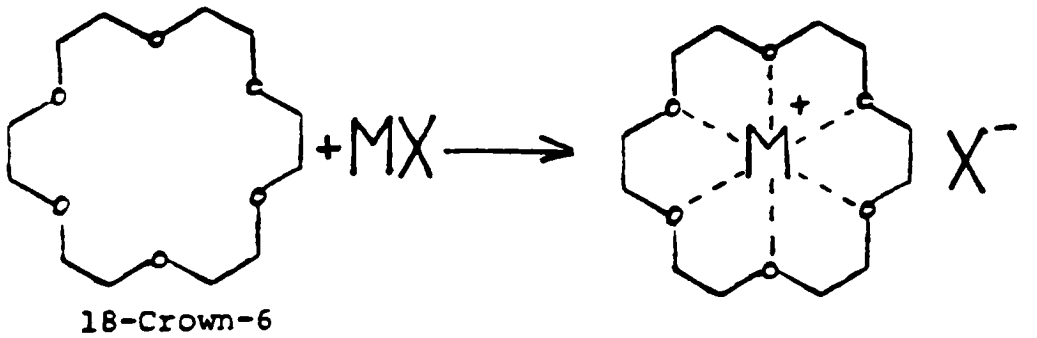
The McConnell-Robertson equation supports the fact that as the distance between the lanthanide cation and substrate increases the induced shift decreases (assuming θ remains constant). Furthermore, in the lanthanide series, the radial extension of the 4f electrons is small and the 5s and 5p electrons shield the lanthanide from the incoming ligand. Therefore, it seems reasonable to say that a pseudocontact interaction would take place rather than a true contact interaction(6).

As mentioned earlier, it is desirable for the lanthanide shift reagent to be soluble in nonpolar solvents. We propose that one way to achieve this solubility is to employ crown ethers. Crown ethers are macrocyclic ethers of ethylene glycol and are named as follows:

18-crown-6 is one example of such an ether where 18 represents the number of ring atoms and 6 represents the number of heteroatoms in the ring(8).

Crown ethers, having the appropriate cavity size have the potential for encapsulating metal cations. These interactions are due to coordinate covalent bonds where each oxygen atom donates a pair of electrons to the positively charged metal ion. Furthermore, the oxygen atoms are coplanar and symmetrically distributed in the coordinated ring(6).

Once this metal complex is formed, the metal cation has the capability of being soluble in a nonpolar solvent due to its newly formed, hydrocarbonlike exterior



18-Crown-6

Equation #3

This phenomenon was first illustrated by Sam and Simmons(9) in 1972. "Purple benzene" produced by the18-crown-6 /$KMnO_4$ complex caused potassium permanganate to be suprisingly soluble in this nonpolar solvent. Thus oxidation reactions could be carried out much more rapidly than usual.

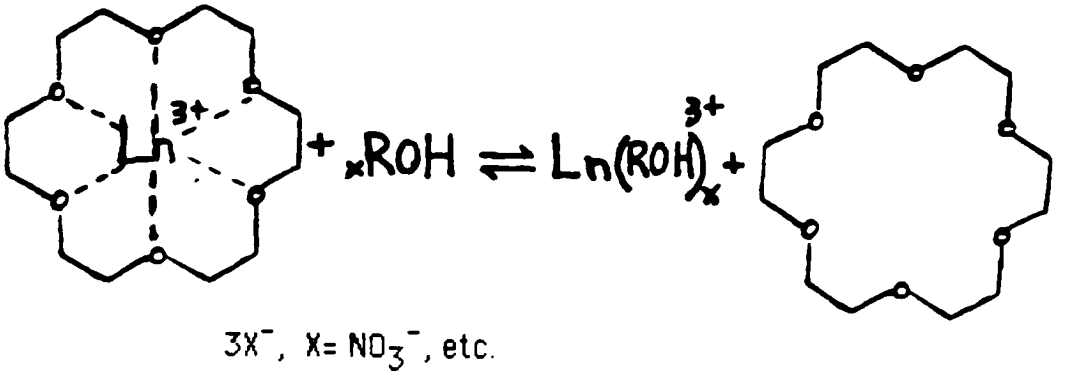
This concept could be extrapolated to lanthanide metal cations.

One might assume that once the lanthanide metal is encapsulated in the crown ether, it would still maintain its formal 3+ charge, (since the crown ether and metal cation are attached by electrostatic non-directional bonds due to the effective shielding of their 4f valence electrons)(6), allowing it to successfully interact (if soluble in an NMR solvent) with Lewis-basic organic substrates and induce shifts in the nuclei of this substrate.

Several lanthanide/crown ether complexes have been synthesized and characterized. For instance, DeCann(6) has characterized the 15-crown-5 $\cdot Pr(NO_3)_3$ complex. Quantitative elemental analysis showed stable 1:1 solid complexes, and the decrease in C-O stretch position by 15-50 cm^{-1} in the IR. Plasma-desorption mass spectrometry was employed to prove that this was a 1:1 (metal:crown) complex in the solid state. Unfortunately this complex was soluble only in polar solvents. Moreover, proton and carbon NMR spectra for the complexed crown nuclei appear at the same resonances as for the free crown. In addition, UV-VIS spectrometric data for the crown complexes give the same band intensity and positions as those for the free lanthanide salts. Finally, when the complex was employed as a lanthanide shift reagent in polar solvents, the induced proton shifts for a solution of a tripeptide with a Pr(III) $\cdot$15-crown-5 complex were identical to those for the tripeptide due to $Pr(NO_3)_3$ only. Thus all experimental results support the fact that this complex dissociated in solution.

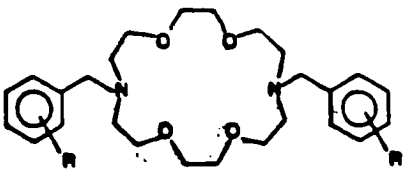
In summary, it seems that a polar solvent promotes dissociation of the highly ionic bond between the 3+ cation and the nitrate anions.

This is illustrated in Equation#4. Thus the high lattice energy of multiply charged metal ions is not easily overcome by the macrocyclic ligand.



Equation#4

Gokel and co-workers(10) have researched the field of macrocycles heavily, specifically the field of "bibrachial lariat ethers" or BiBLES for short. These macrocycles (Fig.#2a) are unique in that their side arms enhance cation binding relative to simple monocyclic crown ethers. These sidearms participate intramolecularly in the cation binding process in both the solution and solid state, and exhibit highly dynamic behavior. Thus the cation is capable of arranging the available donor groups, contained in the sidearms, about itself to obtain the most favorable coordination geometry. As a result, the "hole-size selectivity rule" is less significant, at least for these structures, than had been previously assumed.



Figure#2a

Moreover, Gokel and co-workers(10) have produced a mobile nitrogen-pivot bibrachial lariat ether that can achieve 3-dimensional binding to a metal cation. It has been shown that binding constants for sidearms attached to a nitrogen pivot atom are higher than those for a carbon pivot atom. In addition, results suggest that diazacrowns containing polar donor groups will interact more strongly with a charge dense cation, for example Ca^{2+} as opposed to Na^{+}, than with the solvent due to an ion-dipole interaction, thus decreasing solvent dependency.

In 1983, Hiroshi Tsukube(11) reported that lipophilic macrocyclic polyamine carriers mediated efficient ammonium-cation transport with characteristic properties not observed in previously reported crown ether systems. The hexaaza and tetraaza macrocycles (shown in Figure#3) were selective for ammonium cations over potassium cations as opposed to a typical crown ether which was less selective among cations. Tsukube suggests that the donor sites play an important role in the selection process since the cavity size of the carriers cannot distinguish between the cations to be transported. To make this

observation complete, the crown ethers containing both oxygen and nitrogen donor atoms exhibited transport properties intermediate between those of the polyamine and polyether-type carriers.

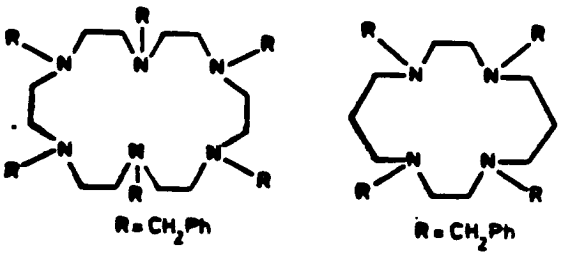


Figure 3

In addition, Tsukube knew that co-transported anions have an affect on the cation transport rates. For example, the rates of transport for mixed-donor type crown ethers and oxygen-only crown ethers require ClO_4^- and SCN^- for the promotion of interfacial cation-binding. However, the hexaaza and tetraaza crown ethers under investigation effectively transported the cation, namely ammonium, in the absence of these hydrophobic anions. Hiroshi Tsukube(11) states that although the mechanistic details are vague, the results suggest that the host cation is more tightly bound to the nitrogen atoms of the polyamines as opposed to the oxygen atoms of the polyethers.

Due to the desirable properties (greater coordination strength) of nitrogen containing macrocycles, over typical polyethers, the field of lanthanide metal/nitrogen containig macrocyclic complexes and their potential as proton NMR shift reagents has been investigated.

Although simple interpretations of lanthanide shifts have proven

to be most useful, structural inferences regarding the LSRs must be considered, for instance, the low symmetry of the lanthanide complexes and their lability as mentioned earlier Most lanthanide complexes have a C_2 axis and therefore the complete form of the dipolar equation can be employed to determine induced paramagnetic shifts as shown below (Equation#5). This is a more complete version of the McConnell-Robertson equation.

$$\Delta\nu = D_1\left\langle\frac{3\cos^2\theta - 1}{r^3}\right\rangle + D_2\left\langle\frac{\sin^2\theta\cos 2\phi}{r^3}\right\rangle \qquad \text{Equation\#5}$$

Where r, θ, and ϕ are polar coordinates of the nucleus under investigation relative to the magnetic susceptibility axes, and D_1 and D_2 are coefficients that depend on the anisotropy of the magnetic susceptibility of each lanthanide complex. However, these coefficients are measured most often as unknowns in a best-fit treatment that includes the orientation of the axes that do not coincide with the symmetry axis, if there even is one present(12).

To add to this confusion, the lability of these complexes produces induced paramagnetic shifts that are determined as a result of an average over all the possible structures of the complex not to mention that the geometric isomers are most likely not axially symmetric(12).

One alternative to the problems mentioned above, is to synthesize a lanthanide complex having structural features such that rigidity and stability are maintained(12).

Desreux and co-workers(12) have done extensive work in this area. One ligand in particular, 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''- tetraacetic acid, DOTA for short (Fig.#3a), has shown to be the most stable lanthanide chelate so far as supported by stability constants. This ligand is remarkably rigid, highly symmetric, and adopts the same geometry in solution as in the solid state. The steric requirements of the 12-membered ring is thought to be responsible for the lack of lability.

Figure#3a

Note that the internal cavity of the DOTA ring is too small to accommodate a lanthanide ion. Thus, DOTA forms a shell around the Eu^{3+} cation only when it is attached to four nitrogen atoms and to four carboxyl oxygen atoms, and one water oxygen atom giving the appearance of a distorted capped square antiprism(12).

In 1979, Hart and co-workers(13) illustrated that the template condensation of 2,6-diacetylpyridine with ethylenediamine gives 18-membered hexa-aza-macrocycle complexes of the type $[M(NO_3)_3L]$ where M=La or Ce and L=2,7,13,18,-tetramethyl-3,6, 14, 17, 23, 24-hexaazatricyclo[17.3.1.$1^{8,12}$]tetracosa- 1(23), 2, 6, 8, 10, 12(24), 13, 17, 19, 21-decaene. The geometry of the lanthanum complex has

been proven by X-ray diffraction. The complexes are kinetically stable in water with respect to dissociation of the macrocycle. The Ce^{3+} complex in particular has proven to be a potential aqueous NMR shift reagent. Unfortunately the heavier lanthanides (Pr-Dy) did not give analogous complexes under the same conditions.

Radecka-Paryzek(14) in 1981, concluded that only the lighter lanthanides (Ce, Pr, Nd) were effective templating agents in the 18-membered macrocycle and that the heavier lanthanide cations (Tb, Dy, Ho, Er, Tm, Yb, and Lu) having a smaller ionic radius were effective templating agents for a 14-membered quadridentate hexa-aza-macrocycle shown below.

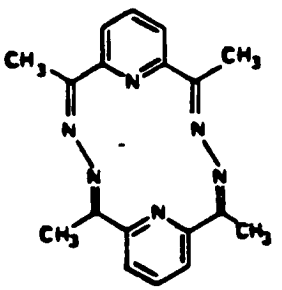


Figure 4

However, Fenton and colleagues(14) illustrated that an 18-membered complex $[M(C_{18}H_{20}N_6O)(NO_3)_3]$ formed via the template condensation of 2,6-pyridinedicarboldehyde with ethylenediamine in the presence of a lanthanide nitrate is independent of the ionic radius of the metal cation. All of the lanthanide cations tried were successful templating agents. All lanthanides except radioactive Pm were tried.

Upon analysis of the characterization data two structures representing the 16-membered macrocycle were determined and are shown below.

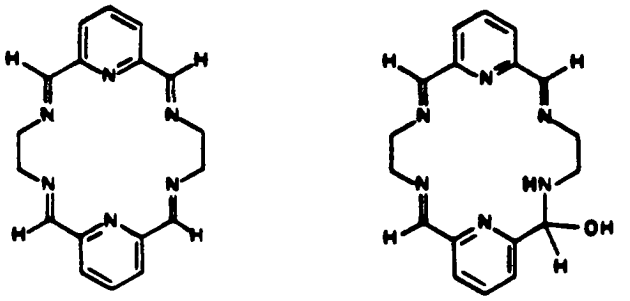


Figure #5

The authors concluded that the complex containing the heavier and smaller radius lanthanide (Nd to Lu, except Eu and Pm) readily adds water to gain flexibility to enable complexation to occur On the other hand, the complex containing the lighter and larger radius lanthanide (La to Pr, and Eu) does not exhibit the presence of a water molecule. Fenton presumed that this is due to a cavity-fit basis, in other words the lanthanide ionic radius and cavity diameter of the macrocycle are compatible(14).

Recently Hart(15) and co-workers illustrated that the complexes of the type $[\{M(NO_3)L(H_2O)_2\}_2]NO_3[ClO_4]_3 \cdot 4H_2O$ could be synthesized with the heavier lanthanides where M= Nd,Sm, Eu, Gd, Td, Dy, Ho, or Er, by a ligand exchange reaction.

Vallarino and co-workers(16) have illustrated that the 16-membered hexaaza macrocyclic ligand (Fig.#9 below) having the

formula $C_{22}H_{26}N_6$, can be formed via the templating effect with any one of the lanthanide cations along with the condensation of 2,6-diacetylpyridine and 1,2-diaminoethane. Again radioactive Pm was apparently not tried. Vallarino stated that the considerable contraction in ionic radius (La^{3+}, 1.061 A to Lu^{3+}, 0.85 A) along the $4f^n$ series does not inhibit the metal cation from acting as a templating agent. The formation of the macrocyclic ligand seems to be dependent upon the counterions present rather than the lanthanide cation. Vallarino also stated that oxygen donor anions, such as acetate, facilitate the reaction much more readily than chloride and perchlorate anions. Following the complex formation, the proper combination of coordinating and noncoordinating counterions, for instance acetate with chloride, isolates the complex in crystalline form.

Moreover, it is suggested that the macrocycle hinges at the two flexible $-CH_2-CH_2-$ side chains forming a "folded butterfly" structure. The dihedral angle between the wings is thought to be 114^0 It is not known if the folding of the macrocycle is due to the ionic radius of the lanthanide cation or by the steric requirements of the hetero-ligands(17). The anions are allowed to coordinate to the metal cation from above and below(15).

These complexes are very interesting due to their solubility in nonpolar, as well as polar, solvents. Furthermore, the macrocylic moiety apparently remains unaffected even in oxygen donor solvents such as water and dimethyl sulfoxide. Typical lanthanide cation

precipitating agents such as F^-, OH^-, and $C_2O_4^{2-}$ cannot remove the metal ion from the macrocyclic ligand. Finally, these complexes are unusual due to the fact that they undergo reversible thermal dehydration and anion loss through hydrolysis yet maintaining the properties of the macrocyclic moiety up to 240^0 C (16).

In view of the recent work described above in the field of nitrogen containing macrocycles, we proposed that a lanthanide metal, specifically praseodymium, could be coordinated to a macrocyclic ligand and that such a complex could be a good lanthanide shift reagent.

In summary, this thesis presents the results and explanations of attempts to prepare and characterize new lanthanide shift reagents.

EXPERIMENTAL

All reagents used to synthesize starting materials and complexes were commercially available and purchased from Aldrich Chemical Company,Inc., Fisher Scientific, J.T. Baker Chemical Co., and from K & K Laboratories. Organic solvents and other necessary materials were commerically available and used without further purification.

Infrared spectra for samples were obtained from a Perkin-Elmer 681 spectrophotometer between 4000-600cm^{-1} The solid samples were analyzed as KBr pellets.

Three instruments were employed to collect proton NMR data: General Electric QE-300(300 MHz), Perkin-Elmer R600(60 MHz), and Nicolet NT-200(200 MHz).

Thermogravimetric analyses were obtained from a Perkin-Elmer TGS-2 instrument heated at a rate of 20 degree/min. under nitrogen gas at a flowrate of 55 ml/min.

Magnetic susceptibility data were obtained from a Johnson Matthey balance at room temperature.

All mobile phase ratios for TLC were prepared in volume/volume ratios.

Melting points were determined using a Mel-Temp apparatus and are uncorrected.

In general L refers to 2,7,13,18,-tetramethyl-3,6,14,17, 23, 24-hexaazatricyclo[17.3.1.$1^{8,12}$]tetracosa-1(23), 2, 6, 8, 10, 12(24), 13, 17, 19, 21-decaene

Model Lanthanide Shift Reagent Experiment

The compounds 3-*endo*—acetoxy-5-*exo*-[2,4-dinitrophenylthio]nortricyclene and its *exo*-acetoxy isomer had been previously synthesized and characterized(18). Deuterated chloroform was added directly to the sample vials. The samples were weighed into NMR tubes. ^{1}H-NMR (300 MHz, $CDCl_3$) spectra were taken of the samples only. The appropriate amount of $Eu(fod)_3$ for a 1.000 0.3000 (mole ratio ofsubstrate : LSR) and 1.000 : 0.5000 was prepared for both stereoisomers. ^{1}H-NMR for the 1.000:0.3000 (*endo*-acetoxy isomer:LSR) mole ratio showed chemical shifts δ 9.14 d, 1H(a); 8.5 doublet of doublets, 1H(b); 7.99 d, 1H(c); 6.09 s, 1H(e); 4.37 s, 1H(d); 3.10 s, 3H(f); 2.84 s, 1H(h); 2.12 d, 1H(j); 1.76 m, 3H(i); 0.07 s, 1H(g);

1.25 ppm s, 27H(Eu(fod)$_3$. The 1.000:0.5000 (*endo*-acetoxy isomer LSR) mole ratio showed shifts δ 9.16s, 1H(a); 8.53 d, 1H(b); 8.07 d, 1H(c); 6.50 s, 1H(e); 4.52 s, 1H(d); 3.43 s, 3H(f); 3.00 s, 1H(h); 2.16 d, 1H(j); 1.78 m, 3H(i); and 0.07 ppm s, 1H(g). The letters a-j correspond to the structure shown in Figure #6 left on page 33.

Attempted Preparation of $Pr(NO_3)_3 \cdot 5H_2O$/____ N,N'-dibenzyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (N00-N00) complex

A modified version of DeCann's experimental procedure(6) was followed to synthesize the complex. The reaction mixture was prepared by dissolving 0.0025 moles (1.1 g) of the commercially available N,N'-dibenzyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (Aldrich) crown in 19 ml of methanol. This was added to 0.0025 moles (1.0 g) of $Pr(NO_3)_3 \cdot 5H_2O$ (Aldrich) previously dissolved in 19 ml of methanol. The reaction mixture was stirred at room temperature until the reagents dissolved as much as possible. The pale green solution was then heated on a steam bath for 35 min. until the solution was reduced by one third in volume. A gummy, pale green product was collected and washed using 5 ml portions of cold methanol via vacuum filtration. The sample was dried in an oven at 60^0 C. The sample, weighing 0.9350 g, was collected. Recrystallization proved impossible due to solubility

problems.

A decomposition point of 298^0 C was determined. TLC was performed on silica (Kodak), cellulose (Kodak), alumina (Kodak), and C_{18} reverse phase plates (J.T.Baker) using various mobile phases such as: methanol, ethanol, propanol, pyridine, THF, 1-butanol, and 1-butanol/water However the spot at the origin did not move. IR showed a broad O-H absorption at 3400 cm^{-1} m; sharp C-O band at 1375 cm^{-1} m; weak C=C bands between 1090 and 1035 cm^{-1}; and an out-of-plane C=C band at 805 cm^{-1} w. Since the product was only slightly soluble in D_2O, DMSO, methanol, acetone, and CCl_4, a ^{1}H-NMR spectrum was not feasible. Anal. Calcd. for $C_{22}H_{38}N_2O_4Pr$: C, 53.52; H, 6.52; N, 4.80; Pr, 24.19. Found: C, 10.03; H, 1.82; N, 2.91; Pr, 53.90.

A second attempt was made to synthesize this NOO-NOO complex using a condenser The homogeneous reaction mixture (1 mmole, 0.4426 g of NOO-NOO ligand and 1 mmole, 0.4350 g $Pr(NO_3)_3 \cdot 6H_2O$) was allowed to reflux for 4-6 hrs. A precipitate weighing 0.0972 g was obtained. The properties of this precipitate, which are inconcistent with the expected for the desired final product, were identical to the material produced in the reaction run for a shorter amount of time.

Preparation of $PrL(CH_3COO)_2Cl \cdot nH_2O$ (L=2,7,13,18,-tetramethyl-3,6,14,17,23,24-hexaazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),2,6,8,10,12(24),13,17,19,21-decaene)

A modified version of Vallarino's experimental procedure(16) was followed. One mmole (0.3184 g) of $Pr(CH_3COO)_3 \cdot 3H_2O$ (Aldrich) was dissolved in 20 ml of methanol. This solution was then added to 2 mmole (0.3264 g) of 2,6-diacetylpyridine (Aldrich) partially dissolved in 20 ml of methanol. To this was added 2.0 mmole (0.1202 g) of 1,2-diaminoethene (Fisher Scientific) dissolved in 5 ml of methanol containing 0.100M NaCl. The heterogeneous reaction mixture was allowed to reflux for 4-6 hrs. whereupon the solvent was evaporated (steam bath). Upon addition of 10 ml portions of diethyl ether, crystals formed. The crystals were dissolved in a minimal amount of chloroform and filtered through cotton to remove solid impurities. Dilution with diethyl ether resulted in an off white-pale green sample. A 40% (0.2925 g) yield was obtained.

The product started to turn brown in color at 150^0 C and steadily turned darker brown until it decomposed completely at 330^0 C. The complex was soluble in methanol, DMSO, chloroform, and water TLC was performed on alumina with fluorescent indicator sheets (Kodak), where a mobile phase of 30:70=water:methanol was employed. One spot having a R_f value of 0.78 was produced. A positive chlorine test (ethanolic silver nitrate)(19) resulted. The IR spectrum showed a broad absorption at 3400 cm^{-1} m; C=N band at 1645-1650 cm^{-1} m and a C=-N band at 1585-1595 cm^{-1} m; asymmetric COO^- band at 1540 cm^{-1} m; pair of symmetrical COO^- bands at 1445 m and 1430 cm^{-1} m; and an

OCO mode at 670 cm^{-1}w. ^{1}H-NMR (200 MHz, $CDCl_3$) gave the follwing chemical shifts δ -3.51 s, 3H (OAc); -1.57 s, 12H(CH_3); 2.00 s, 8H(CH_2); 7.90 d, 4H(meta-pyridine); 8.51 t, 2H(para-pyridine), and 9.5 ppm s, 2H(H_2O) . TGA analysis, (run at 20 degree/min, using nitrogen gas at 55 ml/min.), illustrated that between three and four waters of hydration and 0.5 "acetate groups" are lost upon heating. A magnetic moment, taken at room temperature, of 3.3 B.M. was determined via magnetic susceptibility using a Johnson Matthey balance.

Preparation of $PrL(NO_3)_3$

A modified version of Hart's experimental procedure(13) was followed to synthesize the complex. To a solution of 2.25 mmole (0.9789 g) of $Pr(NO_3)_3 \cdot 6H_2O$ (Aldrich) dissolved in a minimal amount of methanol was added 4.5 mmole (0.2706 g) of ethylenediamine (Fisher Scientific). To this, 4.5 mmole (0.7344 g) of 2,6-diacetylpyridine (Aldrich) was added. The mixture, totalling 90 ml of solution, was allowed to reflux for 4-6 hrs. and then allowed to stand overnight (13 hrs.) resulting in a pale green precipitate at the bottom of the flask. The precipitate was collected, washed with cold methanol and dried in an oven at 80^0 C. A 68% (1.0823 g) yield was obtained.

The sample decomposed violently at 260^0 C. The product was soluble in D_2O. A TLC was performed on alumina with fluorescent

indicator sheets (Kodak), using a mobile phase of 30:70= water:methanol, to give a R_f=0.72. IR showed a broad O-H band at 3430 cm^{-1} m; a C=N band at 1650 cm^{-1} m and a C===N band at 1590 cm^{-1}m; NO_2 stretches at 1450 w, 1420 w, and 1340 cm^{-1}w; and an out-of-plane C===C band at 815 cm^{-1}m. ^{1}H-NMR(200 MHz, D_2O) illustrated chemical shifts δ -15.6 s, 4H; 9.9 s, 4H; -8.0 s, 2H; -3.5 s, 8H(CH_3); 9.4 s, 4H(meta-pyridine); 10.1 s, 2H(para-pyridine); and 11.9 ppm broad s, 2H(H_2O).

Preparation of Praseodymium (III) Picrate Hydrate

A modified version of Nakagawa's experimental procedure(20) was followed. The picrate was synthesized by adding 2.5 mmole (1.3g) of praseodymium carbonate (K&K Laboratories) portionwise to 15 mmole (3.4 g) of picric acid (Aldrich) dissolved in 100 ml of hot water (80-90^0 C). The mixture was stirred over a steam bath for approximately 30 min. A pale green precipitate was separated and discarded. The yellow filtrate was placed in an ice bath whereupon yellow-green crystals formed. The crystals were air dried. A 53% (2.7045 g) yield was obtained. This sample was used as described below without recrystallization.

The picrate decomposed at 289^0 C. The product was soluble in DMSO, methanol, and acetone. TLC was performed on alumina with fluorescent indicator sheets (Kodak), using methanol as the developing

solvent, to produce one yellow spot having a R_f=0.4. IR showed a broad O-H absorption at 3450 cm^{-1} m; NO_2 bands at 1620 s and 1540 cm^{-1} s; C=C bands at 1495 w and 1420 cm^{-1} m; $ArNO_2$ band at 1345 cm^{-1} w; broad C-O band at 1270 cm^{-1} m; and a C-N band at 845 cm^{-1} w. ^{1}H-NMR (60 MHz, DMSO-d_6) showed one singlet at δ 8.55 ppm (assumedly due to the six picrate protons).

Attempted Preparation of Praseodymium (III) L(Picrate)

A modified version of Vallarino's experimental procedure(16) was followed. One mmole (1.0234 g) of praseodymium (III) picrate was dissolved in a minimal amount of methanol. To this, 2 mmole (0.3264 g) of 2,6-diacetylpyridine (Aldrich) was added. Next, a 2 mmole (0.1202 g) solution of 1,2-diaminoethane (Fisher Scientific) containing 0.100M NaCl was added to the reaction mixture which totalled 45 ml of solution. The resulting, homogeneous, orange, reaction mixture was allowed to reflux for 5 hours whereupon a rust colored precipitate formed (0.8870 g).

Diethyl ether was added to the filtrate until a yellow precipitate formed. The precipitate was dissolved in choloroform. Solid impurities were removed by filtration, and the product was precipitated upon addition of ether. The precipitate, weighing 0.0897 g, was collected.

The rust colored product decomposed at 270^0 C, and the yellow

colored product decomposed at 220^{0}C. Both products were only soluble in DMSO. IR spectra for both products were similar to the praseodymium(III) picrate $\cdot 11H_2O$ IR spectrum. TLC was performed on alumina with fluorescent indicator sheets (Kodak), using methanol as the mobile phase, whereupon both products produced one yellow spot with a R_f=0.4. ^{1}H-NMR spectra (60 MHz, DMSO-d_6) showed one singlet at δ 8.54 ppm for the rust product (assumedly due to the six picrate protons) and a singlet at δ 8.45 ppm for the yellow product (assumedly due to the six picrate protons).

Attempted Preparation of PrL(CO_3)Cl

A modified version of Vallarino's experimental procedure(16) was followed. One mmole (0.6059 g) of $Pr_2(CO_3)_3$ (K & K Laboratories) was partially dissolved in 20 ml of methanol. To this stirred slurry, 2 mmole (0.3264 g) of 2,6-diacetylpyridine (Aldrich), dissolved in 20 ml of methanol, was added. Next, 1 mmole (0.1202 g) of ethylenediamine (Fisher Scientific), dissolved in 5 ml of methanol containing 0.100M NaCl, was added to the heterogeneous mixture. The reaction mixture was allowed to reflux for 4-6 hrs. A light green precipitate formed and was collected. An excess of diethyl ether was added in portions to the filtrate until a beige colored precipitate formed. This precipitate was then dissolved in chloroform and solid impurities were removed by filtration. Diethyl ether was added to obtain the precipitate once again.

IR for the light green product showed a broad O-H band at 3460 cm^{-1} m and a pair of strong bands at 1510 assym. and 1430 symm. cm^{-1} representing COO^- stretches. The product was slightly soluble in D_2O, DMSO, $CDCl_3$, and CCl_4. TLC was run on alumina with fluorescent indicator sheets (Kodak) and Baker C_{18} reverse phase plates using 100% ethanol as the mobile phase. The sample spots at the origin did not move. ^{1}H-NMR(200 MHz,DMSO-d_6) δ 3.4 ppm (due to solvent).

The beige colored product decomposed at 380^0 C. The product was soluble in D_2O and DMSO. IR showed a medium to weak asymmetric COO^- stretch at 1640 cm^{-1}; a medium to weak C===N band at 1575 cm^{-1}; and a medium to weak symmetrical COO^- band at 1450 cm^{-1} ^{1}H-NMR (200 MHz, DMSO-d_6) δ 7.3-8.0 ppm, m, aromatic region; 2.5-4.0 s (due to solvent); 1.3-1.5 ppm (due to solvent).

Preparation of Hydrated Praseodymium Chloroacetate

A modified version of Ouchi's experimental procedure(21) was followed. Praseodymium(III) hydroxide was synthesized first by mixing 2 mmole (0.7107 g) of praseodymium(III) chloride (K & K Laboratories) and 6 mmole (0.2400 g) of sodium hydroxide (J.T. Baker) in a minimal amount of distilled water. Upon the addition of sodium hydroxide, praseodymium hydroxide precipitated and 6 mmole (0.3700 g) of chloroacetic acid was added to the reaction mixture. The reaction

mixture was stirred for several minutes over a steam bath. The light green precipitate was collected. A yield of 0.2295 g of praseodymium chloroacetate was obtained.

The light green precipitate turned to a light brown color at 400^{0}C. The product was slightly soluble in D_2O, DMSO, $CDCl_3$, and CCl_4. TLC was performed on alumina with fluorescent indicator (Kodak) and silica sheets (Kodak) using a 50:50=water:methanol mobile phase. The spots at the origin did not move. The IR spectrum showed a broad O-H absorption at 3400cm^{-1} m; two strong COO^- bands at 1580 asymm. and 1420 symm. cm^{-1}; CH_2Cl wag at 1250 cm^{-1}m; and a C-Cl stretch at 790 cm^{-1} m.

Preparation of $PrL(O_2CCH_2Cl)_3$

A modified version of Vallarino's experimental procedure(16) was followed. One mmole (1.3545 g) of praseodymium chloroacetate was partially dissolved in approximately 20 ml of methanol. Two mmole (0.3264 g) of 2,6-diacetylpyridine, dissolved in 20 ml of methanol, was added to the reaction mixture. Lastly, 2 mmole (0.1202 g) of 1,2-diaminoethane was added. The green-yellow heterogeneous mixture was allowed to reflux for 4-6 hrs. A pale green precipitate (0.3161 g) was collected. A 23% yield was obtained. Diethyl ether was added to the filtrate to produce a beige precipitate. The precipitate was then dissolved in chloroform and solid impurities were filtered. Ether was

added again to reprecipitate the product which produced a 73% (1.0406 g) yield.

The green product turned to a tan color at 360^0 C. The product was slightly soluble in methanol, acetone, and CCl_4. IR showed a broad O-H band at 3450 cm^{-1} m; two strong COO^- bands at 1580 asymm. and 1420 symm. cm^{-1}; CH_2Cl wag at 1250 cm^{-1}m; and a C-Cl stretch at 790 cm^{-1}m.

The beige product decomposed at 239^0 C. The product was soluble in D_2O and DMSO. TLC was performed on alumina with fluorescent indicator sheets (Kodak) using a 30:70 = water:methanol mobile phase to produce one spot having a R_f=0.78. IR showed a broad O-H band at 3400 cm^{-1} m; C=N band at 1645 cm^{-1} m and C===N band at 1590 cm^{-1}m; COO^- band at 1560 asymm. m and 1430 symm. cm^{-1} m; CH_2-Cl wagging mode at 1260 cm^{-1} m; and a C-Cl band at 770 cm^{-1} w. ^{1}H-NMR(200 MHz, D_2O) for the product illustrated chemical shifts δ 17.4 d, 4H(meta-py); 15 t, 2H(para-py); 6.3 s, 12H(CH_3); 4.4 s, 8H(CH_2), and 3.5 ppm s, 6H(O_2CH_2Cl). Anal. Calcd. for $C_{28}H_{32}N_6O_6Cl_3Pr$: C, 42.21; H, 4.02; N, 10.55; Cl, 13.38; Pr, 17.71. Found: C, 26.48; H, 3.48; N, 7.39; Pr, 31.9.

Attempted Preparation of the Free Hexaaza Macrocyclic Ligand, L

A stoppered flask containing 20 ml of tetrahydrofuran (Baker) was weighed. An excess amount (2.2458 g, 0.06592 moles) of anhydrous

HCl gas was bubbled into the flask and immediately reweighed. The $PrL(NO_3)_3$ complex (6.594 x 10^{-4} moles) was added to the solution. The solution was heated and stirred continuously for approximately 2 hrs. Approximately half (0.1757 g) of the off white precipitate was set aside to characterize. It turned gray-green in color as it air dried. Sodium bicarbonate (Fisher Scientific) was added to the solution over the remaining precipitate until fizzing ceased. A precipitate (4.3698 g) was collected and turned purple in color as it air dried.

The gray-green precipitate decomposed completely at 300^0 C. The precipitate was soluble in D_2O, DMSO and methanol. TLC was performed on alumina with fluorescent indicator sheets (Kodak) using a 30:70=water:methanol mobile phase giving a R_f=0.78. IR showed a C=O absorption at 1710 cm^{-1} m; C=N band at 1680 w and 1510 cm^{-1} m; NO_2 stretches at 1390 m, 1365 w, and 1310 cm^{-1} w; symmetric C-O-C band at 1240 cm^{-1} w; and symmetric C-O-C bands at 1030 m and 1005 cm^{-1} m. ^{1}H-NMR (200 MHz, D_2O) chemical shifts δ 8.3 ppm s, aromatic region) and 3.4 ppm (methylene region).

The purple precipitate turned to a beige color at 400^0 C. It was soluble in D_2O, turning the clear D_2O solution purple, but left a white precipitate behind. IR of the purple precipitate showed only a sharp absorption at 1390 cm^{-1} m. ^{1}H-NMR (200 MHz, D_2O) illustrated chemical shifts δ 4.78 ppm (due to solvent) ; 0.01,0.07, 1.8. and 2.9 ppm (DSS internal reference).

Lanthanide Shift Reagent Experiment

A lanthanide induced shift study was carried out in the following manner. The LSR solid was weighed in an NMR tube and dissolved with the appropriate solvent. The amount of LSR and solvent used was dependent upon the type of instrument employed. For example, when the Nicolet NT-200 NMR was employed, approximately 20 mg of LSR and 1 ml of solvent was required in order to obtain substantial signals. Once the LSR was dissolved, the required amount of organic substrate, depending on the molar ratio of LSR:substrate to be studied, was added.

RESULTS AND DISCUSSION

A lanthanide shift reagent with a long history of successful applications(5), $Eu(fod)_3$, was utilized in a model LSR experiment. The two complex organic substrates to be studied were 3-*endo*-acetoxy-5-*exo*- [2,4-dinitrophenylthio]nortricyclene (Fig.*6 left) and its *exo*-acetoxy isomer (Fig.*6 right).

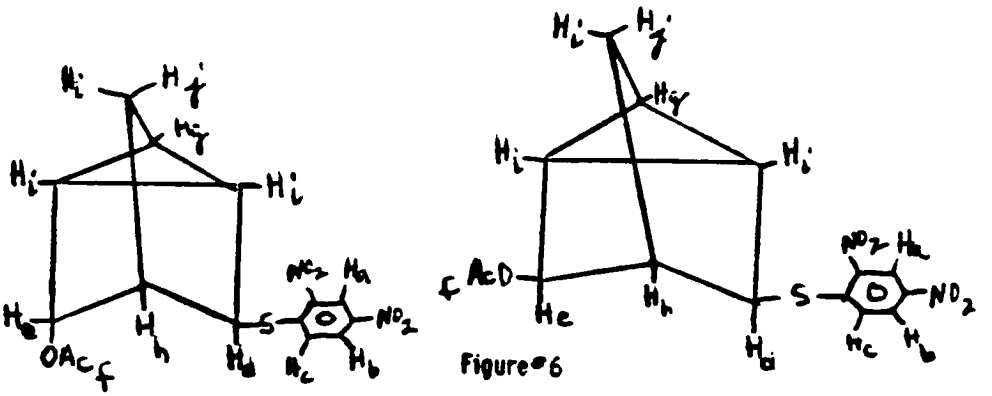


Figure*6

endo-acetoxy/*exo*thioether

exo-acetoxy/*exo*thioether

(Figure *6 coincides with Table*1, 2, and 3).

Table#1: Chemical shifts for the *endo*-acetoxy isomer (Fig. #6 left); QE-300, 300 MHz, in $CDCl_3$

δ ppm	signal	integration	assignment
9.08	doublet	1 H	a
8.40	doublet of doublets	1 H	b
7.75	doublet	1 H	c
3.95	singlet	1 H	d
4.90	singlet	1 H	e
2.14	singlet	3 H	f
0.07	singlet	1 H	g
2.39	singlet	1 H	h
1.66	multiplet	3 H	i
1.99	doublet	1 H	j

Assignments for the aromatic protons a, b, c were made keeping the deshielding effect of the nitro groups in mind. The proton labelled e was assigned further downfield than proton d due to its proximity to the highly deshielding oxygen of the acetoxy group. Protons labelled f were assigned to the acetoxy methyl with the aid of its integration and due to the fact that it's attached to the deshielding acetoxy carbonyl group. Assignments made for protons g-j were determined with the aid of a molecular model to visualize proximity of deshielding groups and with

the help of the integration units.

Two mole ratios of $Eu(fod)_3$ to organic substrate were employed to illustrate the effects of increasing the LSR concentration. The following data (Table*2) were collected for the *endo*-acetoxy isomer.

Table*2 : Chemical shifts for the *endo*-acetoxy isomer (Fig.*6 left) with added LSR: [$Eu(fod)_3$]:[*endo*-acetoxy isomer]; 0.3000:1.000 (QE 300, 300-MHz, in $CDCl_3$)

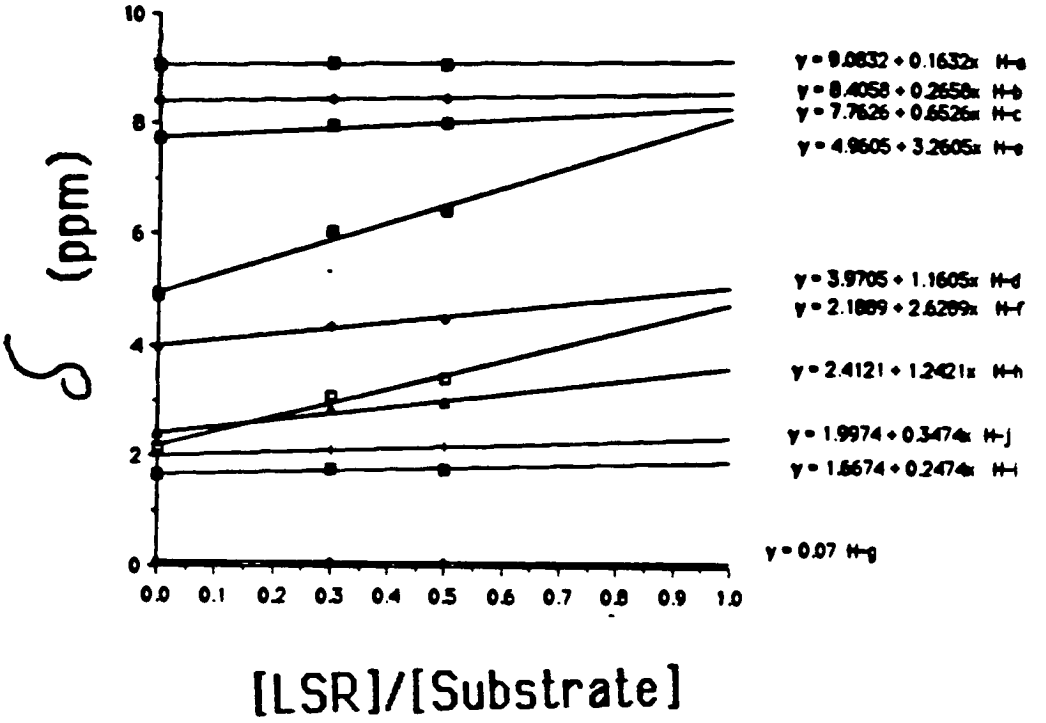
δ ppm	signal	integration	assignment
9.14	doublet	1 H	a
8.5	doublet of doublets	1 H	b
7.99	doublet	1 H	c
4.37	singlet	1 H	d
6.09	singlet	1 H	e
3.10	singlet	3 H	f
0.07	singlet	1 H	g
2.84	singlet	1 H	h
1.76	multiplet	3 H	i
2.12	doublet	1 H	j
1.25	singlet	27 H	$Eu(fod)_3$

Table#3: Chemical shifts for the *endo*-acetoxy isomer (Fig.#6 left) with added LSR: [$Eu(fod)_3$]:[*endo*-acetoxy isomer];0.5000;1.000 (QE-300 MHz in $CDCl_3$)

δ ppm	signal	integration	assignment
9.16	singlet	1 H	a
8.53	doublet	1 H	b
8.07	doublet	1 H	c
4.52	singlet	1 H	d
6.50	singlet	1 H	e
3.43	singlet	3 H	f
0.07	singlet	1 H	g
3.00	singlet	1 H	h
1.78	multiplet	3 H	i
2.16	doublet	1 H	j
1.25	singlet	27 H	$Eu(fod)_3$

Induced chemical shifts of up to 1.6 ppm were observed. Also, as expected, as the concentration of the LSR was increased, the induced chemical shift increased in all cases except for the proton assigned g due to its remote location. Peak assignments in Table#2 and #3 were made keeping the location of the deshielding SAr group and the acetoxy group (coordinated to the LSR), relative to the protons, and the integration units in mind.

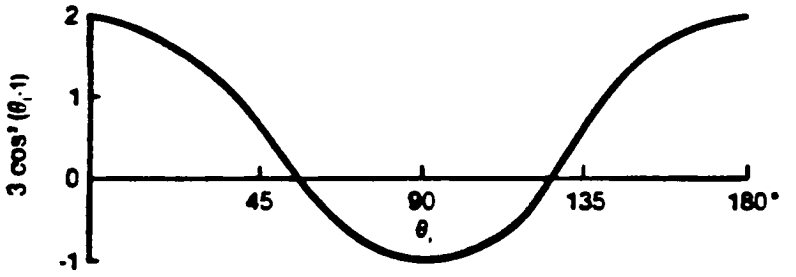
Using the data given in the above tables, a plot of induced chemical shift versus $Eu(fod)_3$ concentration was constructed (Graph# 1). The calculated slopes illustrate the the protons closest to the point of attachment of the LSR to the acetoxy functional group have a greater induced shift as expected from the McConnell-Robertson equation.



Graph# 1

Unfortunately, the data collected for the *exo*-acetoxy isomer (Fig.#6 right) did not prove to be a useful model for a LSR experiment. Problems arose when the induced shift apparently did not increase, in many cases, as the concentration of $Eu(fod)_3$ increased. One explanation for this observation may be rationalized using a modified version of the McConnell-Robertson equation. If the angle θ between r (see page 5) and the magnetic principle axis of the structure is between 54.7^0 and 125.3^0, the induced chemical shift has an opposite sign relative to the other protons in the structure. Thus an induced chemical shift in the opposite direction results. Equation#2 and Figure#7 illustrate this phenomenon. It is not, however, clear why the angle factor would be important for the *exo*-acetoxy isomer and not the other

$$\Delta\delta_{PC} = \frac{K(3\cos^2\theta - 1)}{r^3}$$ Equation#2

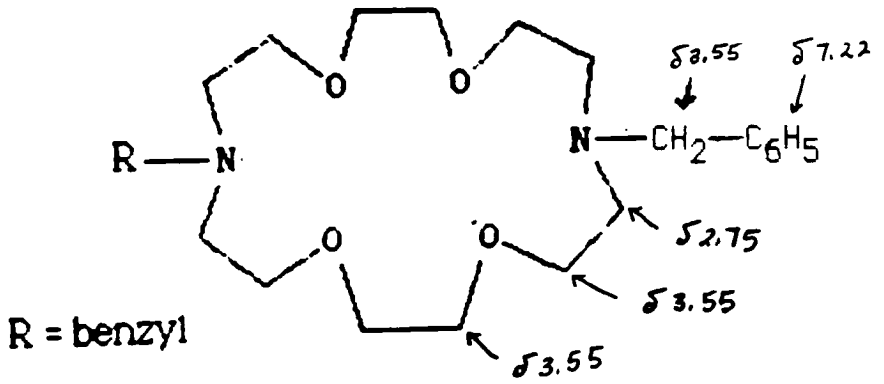


The variation of $3\cos^2\theta_i - 1$ with the angle θ.

Figure#7

The fundamental purpose of our research project was to employ a crown, containing nitrogen atoms, in order to make a lanthanide

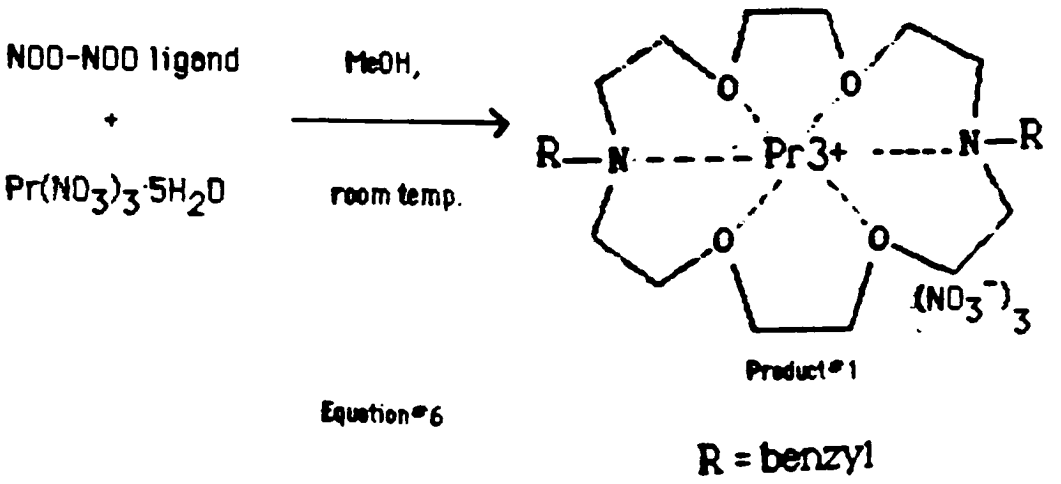
complex. Therefore it was proposed that the crown (Fig.#8) N,N'-dibenzyl- 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane, referred to as the NOO-NOO ligand, would be a useful ligand to ensure complete encapsulation of the lanthanide metal cation; the 3^+ charge on the lanthanide would be maintained due to the neutral character of the crown ligand. We thought that the negative ends of the bond dipoles of the N-CH_2 groups would help keep the lanthanide metal in the crown cavity and that the benzyl groups would cause the complex to be nonpolar and thus soluble in standard nonpolar NMR solvents such as $CDCl_3$.



Figure#8

The NOO-NOO ligand was dissolved in $CDCl_3$ and an NMR spectrum (200 MHz) was obtained. Peak assignments were made (see Fig.#8) with the intent of comparing them to the NMR spectrum of the complex $Pr(NO_3)\cdot 5H_2O$/NOO-NOO since praseodymium was expected to shift resonances in the crown nuclei.

The following reaction was carried out in order to synthesize the $Pr(NO_3)_3 \cdot 5H_2O$/NOO-NOO complex.



Equation #6

This synthesis gave a solid product in 64% "yield." Due to the insolubility of this compound in virtually all solvents, a ^{1}H-NMR spectrum was not obtained. Additional characterization was also unsuccessful. The elemental analysis performed gave a black ash (53.9%) which is thought to be PrO_2. This indicates that the majority of the product is inorganic such as unreacted $Pr(NO_3)_3 \cdot 5H_2O$.

An attempt was made to recrystallize the crude product, once it was synthesized, from a minimal amount of methanol. A melting point attempt showed that the complex decomposed at 298^0 C.

Other solvents were employed to try to recrystallize the crude product since it did not dissolve completely in methanol. Ethanol, propanol, pyridine, THF, butanol, butanol/water, and

methanol/methylene chloride were used. Trituration, and heating methods were tried along with various amounts of the solvents. Unfortunately, the crude product did not dissolve to any appreciable extent in any solvent, and all recrystallization attempts were unsuccessful.

NMR solvents such as: $CDCl_3$, CCl_4, D_2O, acetone-d_6, methanol-d_4, and DMSO-d_6 were used for solubility tests. The complex was again only slightly soluble in all these solvents. When the cloudy NMR samples were analyzed on an R-600 NMR, only chemical shifts for the NMR solvents were observed.

An attempt was made to perform thin layer chromatography on the $Pr(NO_3)_3$/NOO-NOO product. Alumina, silica with fluorescent indicator, cellulose F, and Baker Si-C_{18}F reverse phase glass plates were employed. Various solvents (those mentioned above) and various methods such as heating the TLC chamber and forming a "slurry" of the complex were tried. Unfortunately, only the spot (unmoved) at the origin was observed after TLC development.

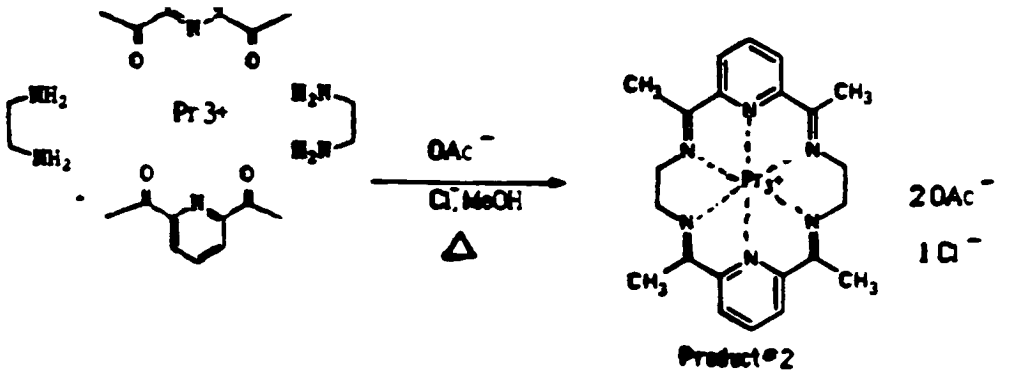
Impurities in the NOO-NOO ligand, the starting material, were suspected due to its off white coloring and observed melting point of 75-77^{0}C vs. the literature value(22) of 80-83^{0}C. Attempts were made to recrystallize the NOO-NOO ligand from methanol, toluene, and hexanes (employing decolorizing carbon); hexanes proved to be the best solvent. After three recrystallizations, a sharp melting point of 75^{0}C was obtained, and one spot on a C_{18} reverse phase chromatography plate

was observed. However, the low melting point suggested that the recrystallized material was not improved in purity, and therefore, it did not seem worthy to synthesize the complex using the recrystallized NOO-NOO ligand.

One last attempt was made to purify the crude complex product using a Soxhlet extraction apparatus containing methanol. The solution was allowed to reflux eight hours a day for four days. TLC was performed using silica, cellulose F, alumina, and reverse phase plates, but the sample spots at the origin did not move.

The insolubility characteristics and purification problems involving the $Pr(NO_3)_3$/NOO-NOO complex suggested that this type of species would not be a manageable shift reagent. We were pleased to be made aware by Dr. Marvin Illingsworth of a hexaaza macrocyclic complex, previously synthesized by Vallarino and co-workers(16). These complexes seemed to have great potential due to their solubility in solvents of a wide polarity range. Moreover, since the hexaaza macrocycles contain more coordinating nitrogen atoms than the NOO-NOO ligand, it seemed even safer to assume that the stability of the lanthanide macrocyclic complex would be greater.

The following synthetic approach was employed to synthesize the complex, $PrL(CH_3COO)_2Cl{\cdot}3H_2O$ where L= 2,7,13,18,-tetra-methyl-3,6,14,17, 23, 24-hexaazatricyclo[17.3.1.$1^{8,12}$]tetracosa-1(23), 2, 6, 8,10,12(24), 13,17,19,21-decaene.



Product#2

Equation#7

This template synthesis is unique in that it is the praseodymium cation that acts as the "template" or guide to bring the individual components together The complex was characterized by decomposition point determination, solubility tests, a positive chlorine test(19), TLC, IR, ^{1}H-NMR, TGA, and magnetic susceptibility. The characterization data were supported by the literature data(16).

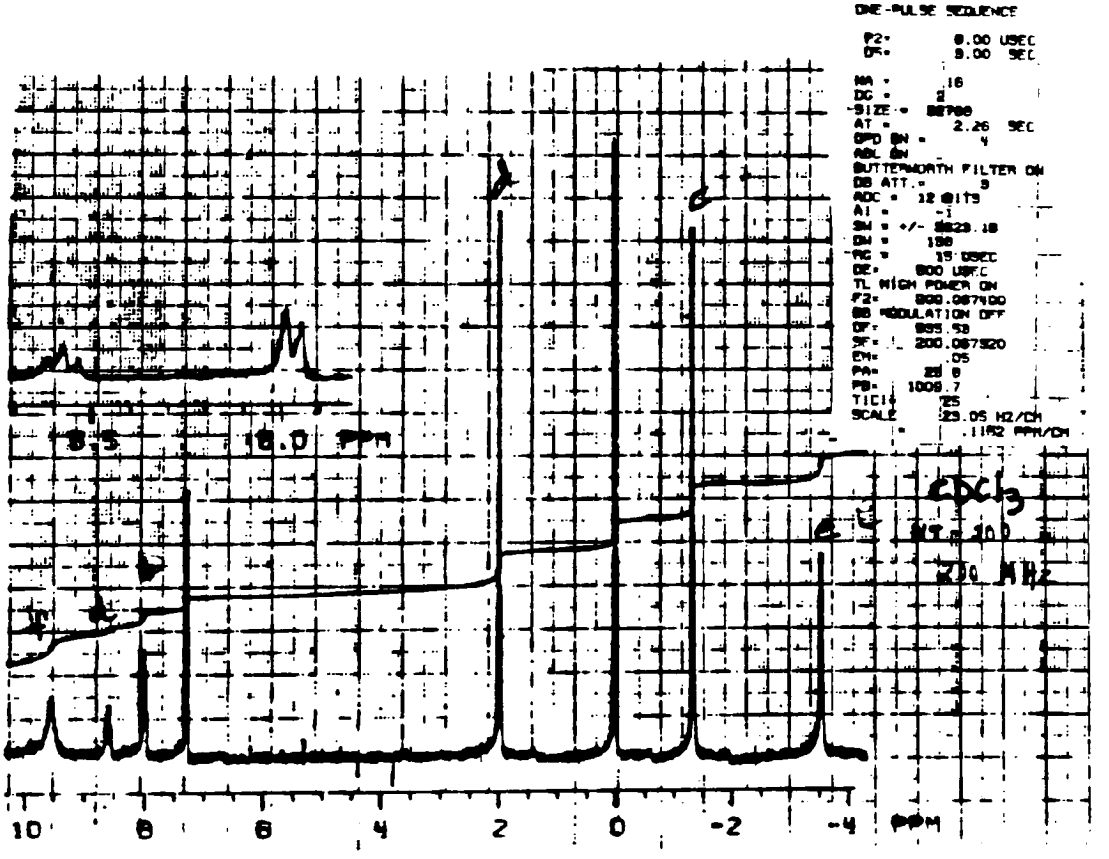
Vallarino and co-workers(16) conclude that the complex contains both ionic acetate, $\nu_a(COO^-)$ at 1550 cm^{-1} and $\nu_s(COO^-)$ at 1430 cm^{-1}, and bidentate chelating acetate $\nu_a(COO^-)$ at 1540 cm^{-1} and $\nu_s(COO^-)$ at 1455 cm^{-1}. They also conclude that the complex contains both weakly coordinated and lattice water giving the lanthanide cation a coordination number of nine. The formula suggested for the complex is $[LnL(CH_3COO)(H_2O)](CH_3COO)Cl{\cdot}nH_2O$ where Ln refers to the lanthanide metal. Table#4 presents the experimental IR data.

Table*4: IR for $[PrL(CH_3COO)(H_2O)](CH_3COO)Cl{\cdot}nH_2O$

wavenumber (cm^{-1})	assignment
3470, 3400, 3300b	OH region
1645-1650m	C=N
1585-1595 m	C=N
1540m, shoulders at 1550 and 1530	Antisymmetric COO^-
pair of bands at 1445m and1430m	Symmetric COO^-
670w	OCO

The ^{1}H-NMR (200 MHz) was carried out in $CDCl_3$ and is shown below (Figure*9 coincides with Spectrum*1).

Spectrum*1: ^{1}H-NMR spectrum of $PrL(CH_3COO)_2Cl{\cdot}nH_2O$



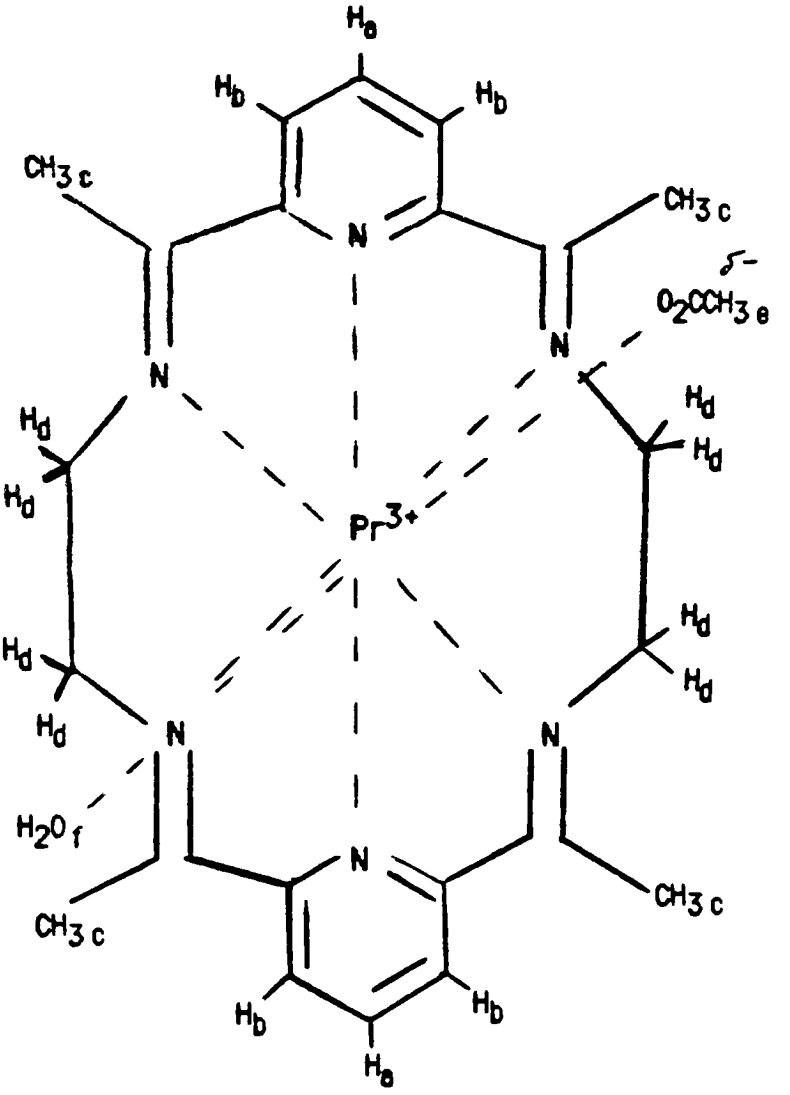
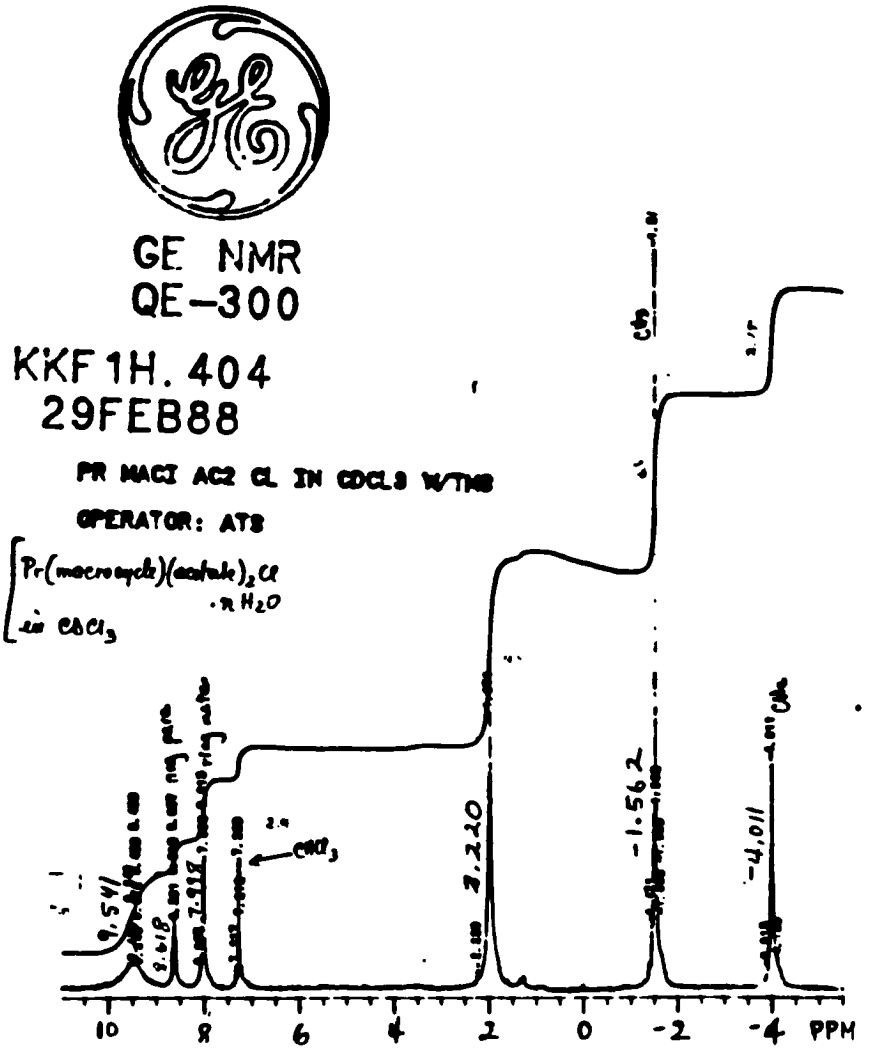


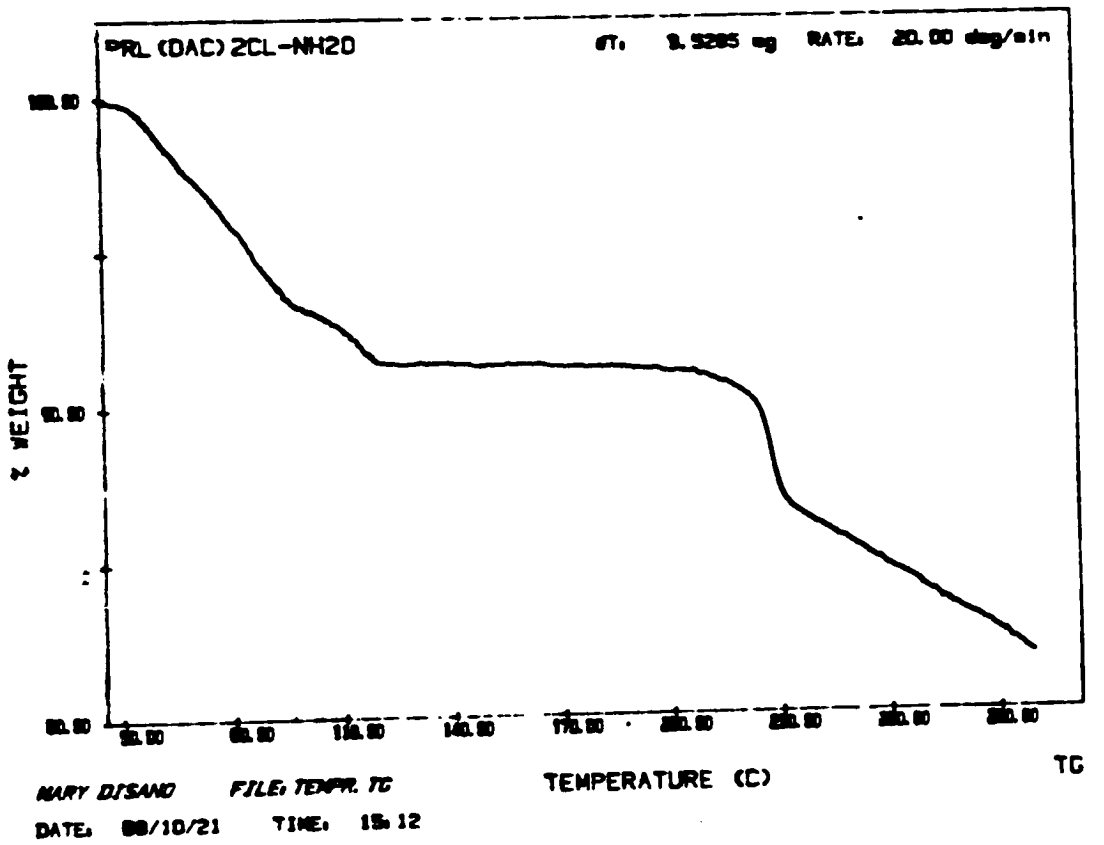
Figure #9

The ^{1}H-NMR spectrum shown below (Spectrum#2) is from the laboratory of Vallarino(16) and represents the complex, $[PrL(CH_3COO)(H_2O)](CH_3COO)Cl{\cdot}nH_2O$ and closely resembles our data.

Spectrum#2: ^{1}H-NMR of PrL$(CH_3COO)_2Cl\cdot nH_2O$ (QE-300, 300 MHz in $CDCl_3$)



Analysis of the thermogram (Figure# 10) illustrates that a cumulative weight loss of 8.6% occurred approximately between 45^0 C and 110^0 C. This value with the sample mass of 3.5285 mg and molecular weight of the original sample (722.5 g) was used to determine that 3.49 molecules of water are lost upon heating the complex. A weight loss of 4.9% occurred approximately between 200^0 C and 230^0 C, corresponding to the loss of 0.56 "acetate groups." The original complex contains between three and four waters of hydration. The acetate results are inconclusive.



Figure# 10

Once the composition of the $PrL(CH_3COO)_2Cl{\cdot}3H_2O$ complex had been confirmed, it was tested as a lanthanide shift reagent using 1-heptanol as the organic substrate. The molar concentrations listed in Table#5 were employed.

Table#5 : Amounts of LSR ($PrL(CH_3COO)_2Cl{\cdot}nH_2O$) and Alcohol in 1 ml $CDCl_3$

[LSR]/[Alcohol]	[LSR]	[1-heptanol]
0.5000 1.500	5.950×10^{-3}M	1.800×10^{-2}M
0.5000 : 1.000	2.980×10^{-3} M	5.950×10^{-3}M
1.000 : 1.000	5.950×10^{-3}M	5.950×10^{-3}M

The only signals that clearly shifted were those belonging to the original LSR complex; specifically the methylene groups attached to the amine backbone should a δ 0.20-0.15 ppm change in chemical shift was observed. This may simply be due to a bulk solvent effect.

The only alcoholic signal that did shift was the hydroxylic proton. Unfortunately, this is likely due to the fact that the position of the hydroxylic proton is dependent upon concentration and thus this shift was not due to the LSR. If the concentration of alcohol is increased, hydrogen bonding is increased. As a result the electron density around the proton is decreased and absorption occurs downfield.

Upon further examination of the [LSR]/[1-heptanol] spectra it appeared that there might be hope for this lanthanide shift reagent. It

was noted that as the LSR concentration increased, the multiplet between δ1.26-1.30 ppm, assigned to the 1-heptanol methylene groups, seemed to be breaking up. Therefore, the LSR concentration was increased to a great extent in the hopes that these signals would separate even more.

Subsequently, another pair of [LSR]/[1-heptanol] experiments were conducted. The following conditions were followed.

Table*6: [LSR {PrL($CH_3COO)_2Cl \cdot nH_2O$}]:[Alcohol]

[LSR]/[Alcohol]	[LSR]	[1-heptanol]
*5.000 : 1.000	9.360×10^{-3}M	1.870×10^{-3}M
^10.00 1.000	8.740×10^{-3}M	8.740×10^{-4}M

*In 2.35 ml of $CDCl_3$

^In 1.25 ml of $CDCl_3$

Unfortunately, additional separation of the multiplet did not occur. The only signals that did show shifts were those small increments for the LSR described above.

Since the LSR effect is due to a Lewis acid-base coordination, a stronger Lewis base such as an amine was studied. We hoped that the electrostatic attraction between the positively charged metal cation and lone pair of electrons on the amine base would be strong enough to induce a shift.

A 1.000 : 1.000 molar ratio of LSR to amine was used. Two amines, diisopropyl and hexylamine, were tested. The former was used

because of its availability, while the latter was used because of its linearity and similarity to 1-heptanol. Once again, the only signals that did shift were those belonging to the LSR, and none of the protons belonging to the amines underwent a shift.

Decomposition or minor alteration over a period of time may explain *why* the LSR chemical shifts were the only ones to move. To test this theory, the NMR spectrum of a sample, prepared in August 1988, was run in October 1988, and was compared to a NMR spectrum of a newly prepared sample run in October 1988. Upon comparison, the spectra were virtually identical. Thus, we can conclude that the complex in solution ($CDCl_3$) is stable over a period of two months.

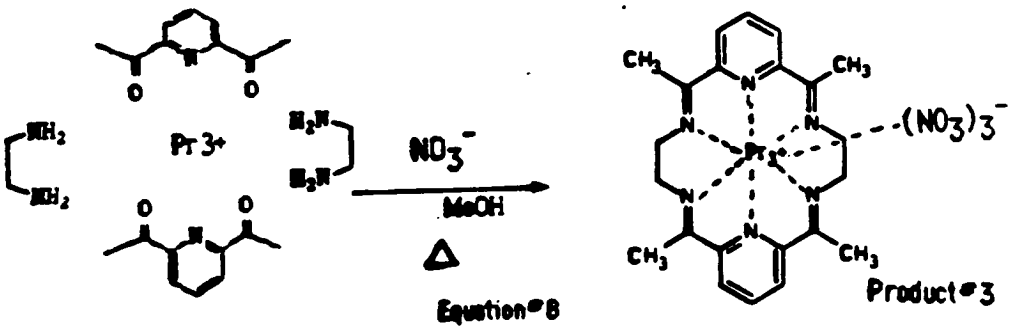
In summary, contrary to Vallarino's reports(16), the $Pr(CH_3COO)_2Cl{\cdot}3H_2O$ complex in our hands did not prove to be a successful lanthanide shift reagent. In order for the complex to be an efficient shift reagent, the lanthanide metal has to be able to coordinate with the Lewis base and our results suggest that this pseudocontact is not taking place. We have speculated that the geometry of the complex is such that the organic substrate is hindered from coming in contact with the metal cation. We thought either the acetate group and/or water coordinated to the cation blocks it from coordinating with an organic substrate such as an alcohol or amine. Moreover, the acetate and water species may be coordinated so strongly to the cation that some of the positive charge may be dissipated by these species, and thus is not available for the incoming organic

substrate. This line of reasoning lead to our efforts to alter the original complex and replace the hindering groups with non-obstructive constituents.

Another logical step was to free the LSR from steric blocking by driving off the coordinated water and then immediately carry out a shift reagent experiment. As described above, TGA results had shown that three waters of hydration could be removed by heating. Preparative scale samples of dehydrated LSR were produced using an Abderjhalen apparatus. The NMR spectra illustrated that the chemical shift assigned to water had diminished. However, when a shift reagent experiment was performed on the sample dehydrated by the Abderjhalen method, no significant shifts were observed.

Assuming that the acetate anion coordinated to the praseodymium was in some way inhibiting the incoming substrate, it seemed appropriate to synthesize the template complex containing different counteranions.

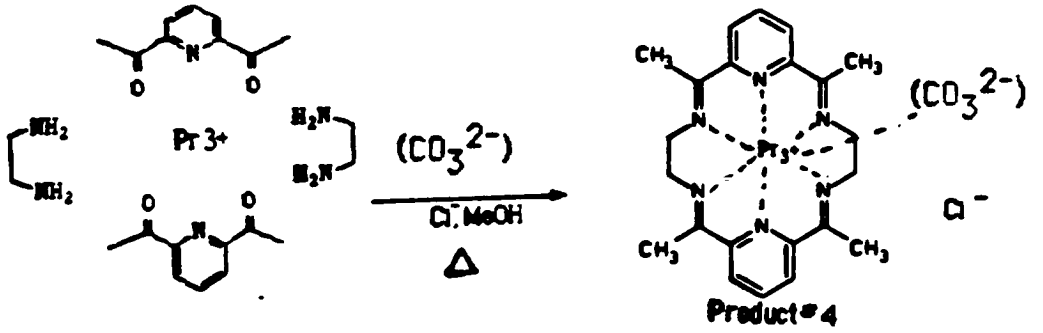
As mentioned earlier Hart and co-workers(13) have reported that the Ce^{3+} nitrate template complex has proven to be a potential aqueous NMR shift reagent. We thought that the nitrate template complex could be synthesized using Pr^{3+} and hopefully it would be a successful LSR. The following reaction scheme was followed to synthesize the praseodymium nitrate template complex.



Equation#8 Product#3

The synthesis gave Product#3 in 68% yield. IR, ^{1}H-NMR, and other forms of analysis suggested that the desired complex had been formed. This product was readily soluble in D_2O but not in organic solvents. The praseodymium complex was tested as a lanthanide shift reagent in D_2O using 1-heptanol as the organic substrate. A one to one ([LSR]/[1-heptanol]) mole ratio was prepared. Unfortunately, none of the protons belonging to the alcohol showed shifts.

An attempt was made to synthesize the template complex by employing commercially available praseodymium(III) carbonate as the lanthanide source. It was presumed that the carbonate anion and chloride ion would balance the Pr^{3+} charge. This is illustrated in the following reaction (Equation#9).

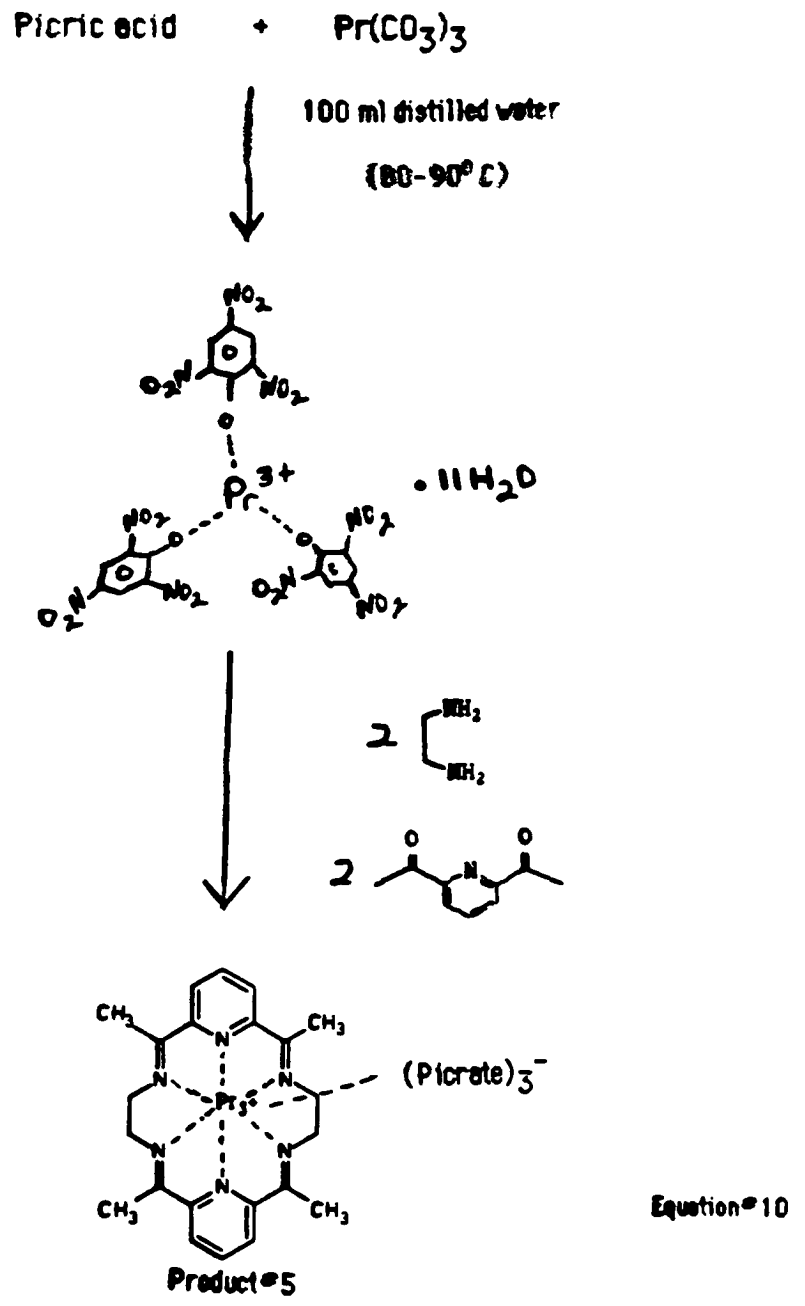


Equation#9

The foregoing reaction was attempted in the usual fashion, and both green and beige products were isolated. ^{1}H-NMR and other forms of

analysis suggested that Product#4 was not formed. For instance, the IR spectrum for the geen precipitate was virtually identical to that for $Pr_2(CO_3)_3$, having a broad O-H band at 3460 cm^{-1} and a pair of strong bands at 1510 and 1430 cm^{-1} representing COO^- stretches. The NMR spectrum of the beige colored product did not illustrate chemical shifts at 8.95 ppm, triplet and at 8.48 ppm, doublet which are characteristic of the macrocyclic ligand. Perhaps the praseodymium(III) carbonate did not react with the starting reagents because the ionic association between praseodymium and carbonate is very strong relative to the driving force for the imine formation of the macrocycle. Both praseodymium and the polyatomic anion (CO_3^{2-}) are charge dense and therefore are strongly attracted to each other

The employment of picrate as the counteranion source for the template complex synthesis seemed reasonable since picric acid, with an acid dissociation constant of 4.2×10^{-1}, is a reasonably strong acid. Thus the picrate anion should be quite weakly basic since the nitro groups are electron withdrawing and would stabilize the phenoxide anion. As a result this anion should not be highly attracted to a positively charged metal ion. Thus it was hoped that the picrate would only weakly associate with the praseodymium 3+ cation and thus less readily compete with an organic substrate for the lanthanide cation. The following synthetic approach to prepare the praseodymium picrate template complex was followed.



Product=5

Equation=10

The synthesis of praseodymium(III) picrate hydrate gave a 66% yield. Its structure was supported by IR, ^{1}H-NMR, and TLC data and were in agreement with the literature values(20). This picrate salt was

then employed in an attempt to synthesize the template complex.

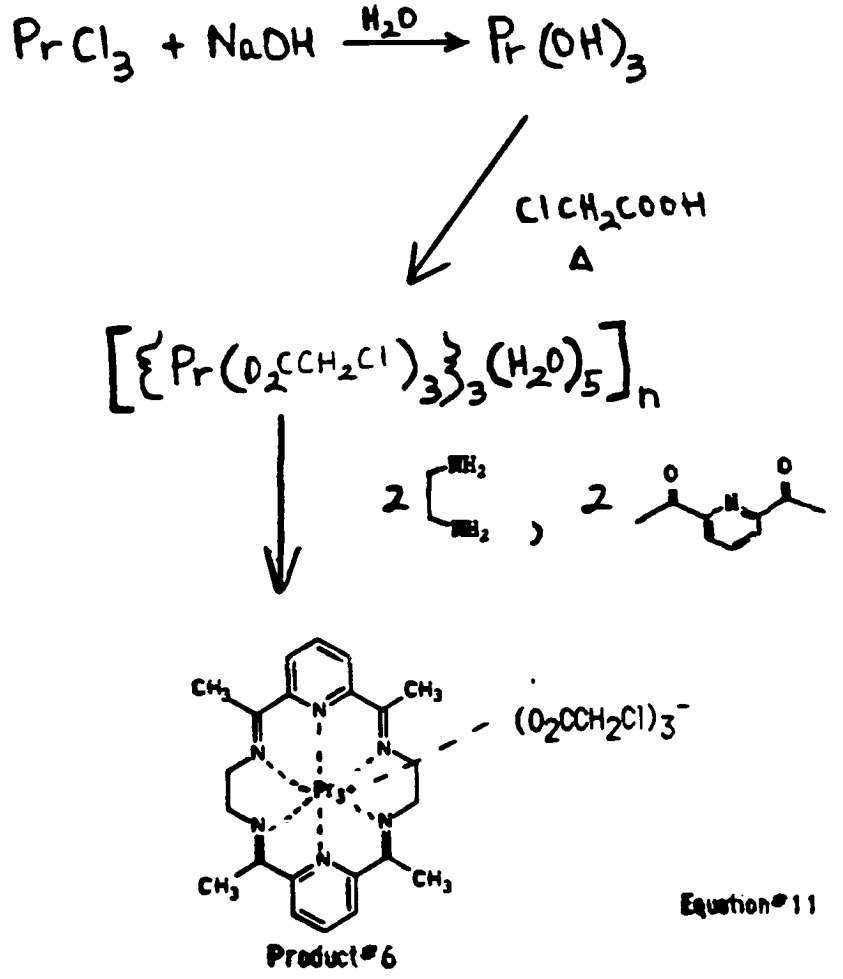
Two products were obtained, and are referred to by their colors: rust and yellow. The reaction was run twice, once with a reaction mixture containing NaCl and once without. The same results were obtained for both reactions. Although, rust and yellow products were isolated, ^{1}H-NMR, IR and other forms of characterization suggested that Product#5 was not formed. Instead, unreacted starting material had been collected.. Additional attempts were made to synthesize Product#5. We assumed that the template formation might be the result of an equilibrium reaction and our variations in reactions were done to take advantage of Le Chatelier's Principle. First, the amounts of reagents (2,6-diacetylpyridine and 1,2-diaminoethane) were doubled in order to drive the reaction to the right. Unfortunately, this attempt did not lead to the picrate template complex. A Dean-Stark apparatus, using benzene as the inert solvent, was employed to remove water as it was produced as a side product forcing the equilibrium to the right. Although there were signs of water production, the rate of reaction was neither even nor controllable. Thus, this approach was discarded.

At this point a new counterion, chloroacetate, was proposed for reasons similar to our earlier choice of the picrate ion. Chloroacetic acid would be used to prepare praseodymium chloroacetate, which in turn woud be used in the synthesis of the template complex containing chloroacetate. The dissociation constants for the various acids put these experiments into perspective. The K_a for chloroacetic acid is 1.40 x 10^{-3} which is between the K_a for acetic acid (1.76 x 10^{-5}) and for

picric acid (4.2×10^{-1}). Thus chloroacetic acid is perhaps a strong enough acid to provide a weak conjugate base allowing it to coordinate with Pr^{3+}, but weak (conjugate base) enough to be displaced by an incoming organic substrate.

Moreover, chloroacetic acid is soluble in water and alcohol as well as benzene, chloroform, and ether Hopefully the solubility properties would carry over to the template complex allowing it to be soluble in nonpolar NMR solvents.

The following synthetic steps (Eq.# 11) were employed to prepare the praseodymium chloroacetate template complex.



Product#6

Equation#11

The synthesis of praseodymium chloroacetate gave 0.2295 g. Its structure was supported by the IR data. The IR spectrum for praseodymium chloroacetate hydrate was virtually identical to the IR for praseodymium acetate hydrate except for the additional CH_2-Cl absorptions at 1250 cm^{-1} and 790 cm^{-1}.

The praseodymium chloroacetate was then employed in an attempt to synthesize the template complex. Two products were synthesized and they are referred to by their colors: pale green and beige. IR and solubility properties for the pale green product were similar to those for praseodymium chloroacetate and this suggested that the pale green product was not templated.

IR and ^{1}H-NMR for the beige product supported the stucture for Product* 6 First, IR showed a C=N band at 1645m cm^{-1} and a C=N(pyridine) at 1590m cm^{-1} that are characteristic of the macrocyclic ligand. Furthermore, the $\nu_a(CO_2^-)$ and $\nu_s(CO_2^-)$ of the free acetate ion is ca. 1560 and 1416 cm^{-1} respectively. Nakamoto(23) reports that in a bidentate (chelate) complex the separation between the $\nu(CO_2^-)$ stretches is smaller than that of the free acetate ion. IR data (Table*7) for the beige product is in line with Nakamoto's(23) findings.

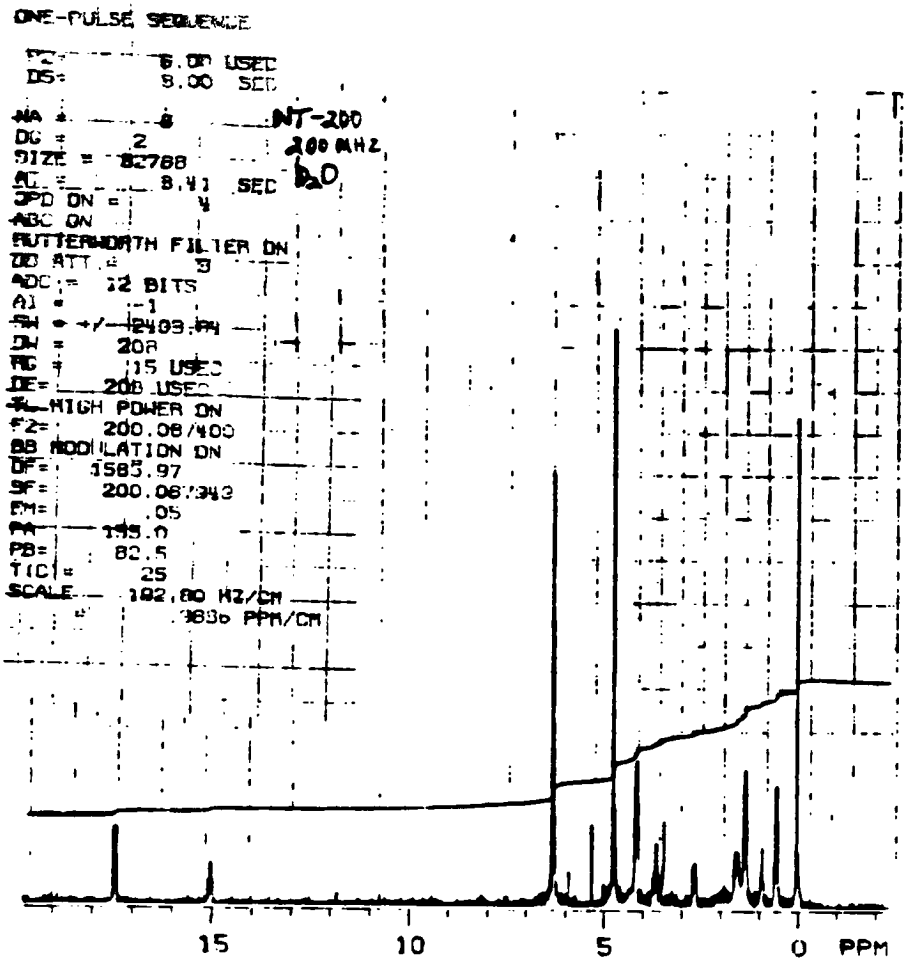
Table*7: IR for praseodymium chloroacetate template complex

wavenumber(cm^{-1})	assignment
3400 broad	OH region
1645m	C=N
1590m	C===N (pyridine)
1555 m	COO^- asymm.
1430m	COO^- symm.
1260 m	CH_2Cl wagging mode
1200m, 1005w	C-H
770w	C-Cl
665w	OCO mode

Secondly, the ^{1}H-NMR spectrum (Spectrum*3) shows chemical shifts at δ 17 4 ppm (d, meta -py) and 15.63 ppm(t, para-py) which are characteristic of the macrocyclic ligand.

One intriguing observation made from the NMR data (Spectrum *3) is that the signals in the praseodymium chloroacetate template complex tend to be farther downfield relative to the $PrL(CH_3COO)_2Cl{\cdot}3H_2O$ complex and does not exhibit any chemical shifts upfield of δ 0.00ppm. Perhaps the chloro group has a great deshielding effect.

Spectrum#3: ^{1}H-NMR for $PrL(O_2CCH_2Cl)_3$ (NT-200, 200 MHz in $CDCl_3$)

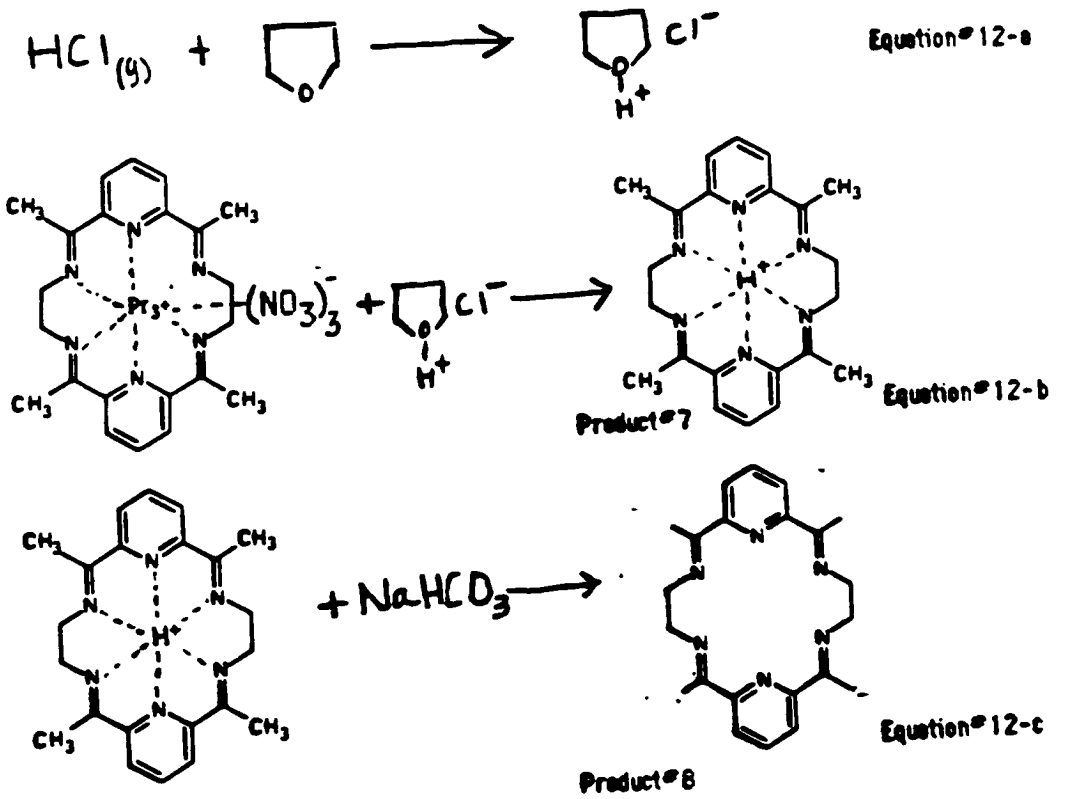


The elemental analysis performed gave a white ash (31.9%); however a white ash does not conform to the CRC handbook(24) regarding the metal oxides of praseodymium. Perhaps some other form of praseodymium, such as $Pr(OH)_3$ and/or praseodymium chloroacetate, is responsible for the white ash. A praseodymium compound could also explain the downfield shifts in the ^{1}H-NMR for the complex. In effect, the ligated macrocycle is being shifted additionally by Pr^{3+} compounds

in the sample.

The beige product was employed as a lanthanide shift reagent using 1-heptanol as the organic substrate. A one to one ([LSR]/[1-heptanol]) mole ratio was prepared. Unfortunately, none of the protons belonging to the alcohol showed shifts.

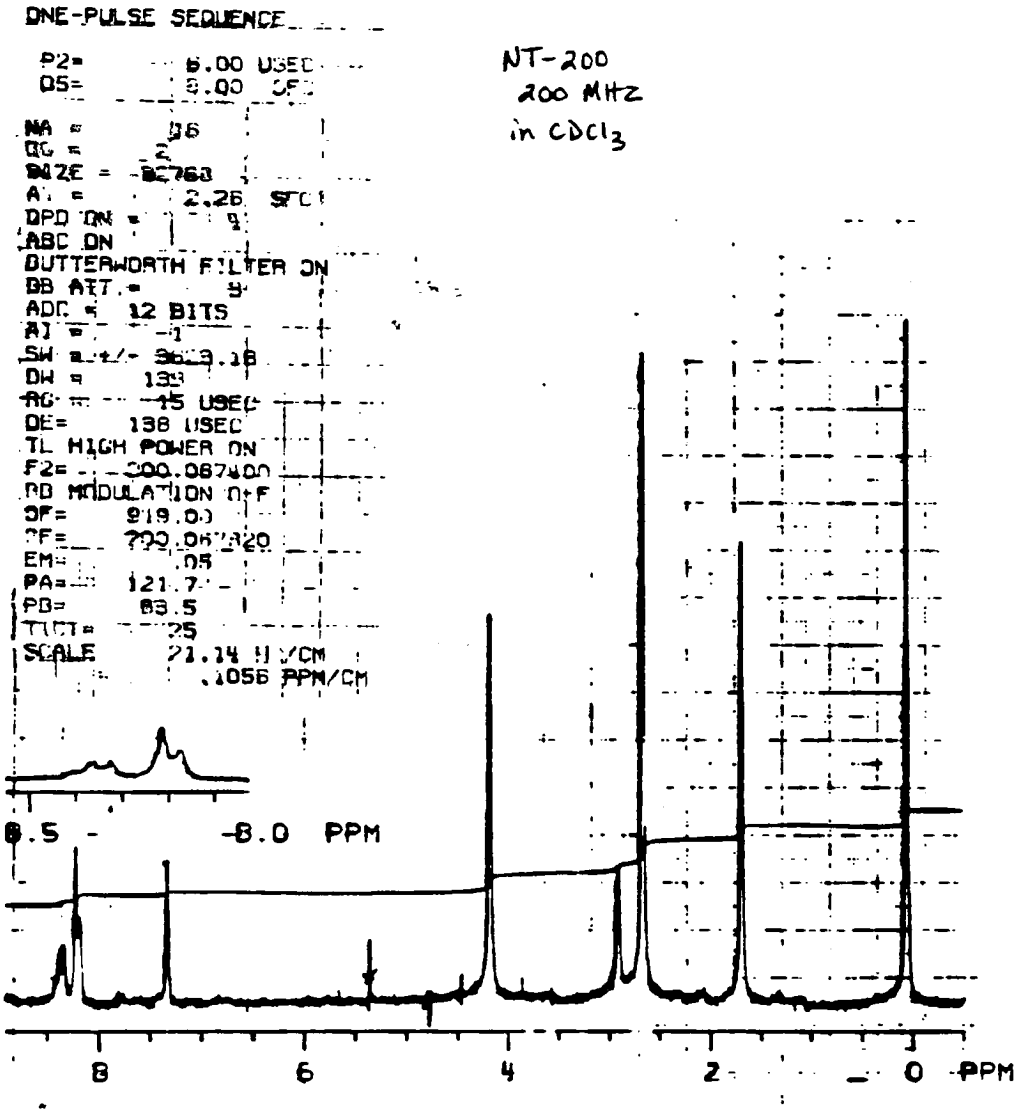
Vallarino(25) has stated that the free hexaaza macrocyclic ligand can not be prepared. It would be beneficial to study the free ligand for many reasons. First, comparing the IR and NMR spectrum for the free ligand and complex would confirm the encapsulation of Pr^{3+} Secondly, induced chemical shifts caused by the lanthanide cation would be elucidated. The following synthetic approach to prepare the free macrocyclic ligand was followed.



The product of eq.12-b was isolated (0.1757 g) and characterized to determine if the starting materials had reacted. IR, ^{1}H-NMR, and TLC suggested that this was not Product#7 containing the macrocyclic ligand coordinated to a proton. The synthesis in step 12-c gave 4.3698 g of solid. IR and ^{1}H-NMR suggested not suprisingly that the free macrocyclic ligand (Product#8) was not synthesized. For instance, medium C=N stretches were not observed in the IR. ^{1}H-NMR did not show chemical shifts (triplet for the para-py and doublet for the meta-py protons) characteristic of the ligand.

Recently, George(26) has prepared the template complex using lanthanum, following Vallarino's(16) procedure. Since $La^{3+}(4f^0)$ does not have unpaired f-electrons, it is neither expected nor found to show lanthanide-induced shifts. Therefore, when the ^{1}H-NMR for the lanthanum complex is compared to ^{1}H-NMR for the praseodymium complex, the coordination of Pr^{3+} to the ligand can be confirmed. The ^{1}H-NMR (Spectrum#4, 200 MHz, $CDCl_3$) spectrum for the lanthanum complex shows no chemical shifts upfield of δ 0.00 ppm whereas the praseodymium complex has two signals upfield of δ 0.00 ppm (δ -3.51 ppm s, 3H, OAc and δ -1.57 ppm s, 12H, CH_3). This suggests that Pr^{3+} is coordinated to the macrocyclic ligand.

Spectrum#4: ^{1}H-NMR for $LaL(CH_3COO)_2Cl{\cdot}nH_2O$ (NT-200, 200 MHz)



Although, no new lanthanide shift reagents were synthesized using the template complex; it is believed that additional non-obstructive counteranions will allow Pr^{3+} to induce chemical shifts in ^{1}H-NMR of organic substrates.

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